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United States Patent [19]

Hayes

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[54] **AUGMENTATION FOR AN ORTHOPAEDIC IMPLANT**

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[73] Assignee: **Zimmer, Inc.**, Warsawm, Ind.

[21] Appl. No.: **200,269**

[22] Filed: **Feb. 23, 1994**

[51] **Int. Cl.**[6] **A61F 2/38**

[52] **U.S. Cl.** **623/20**; 623/11; 623/16; 623/18; 606/72; 606/73

[58] **Field of Search** 623/11, 16–18, 623/20; 606/60, 72–73

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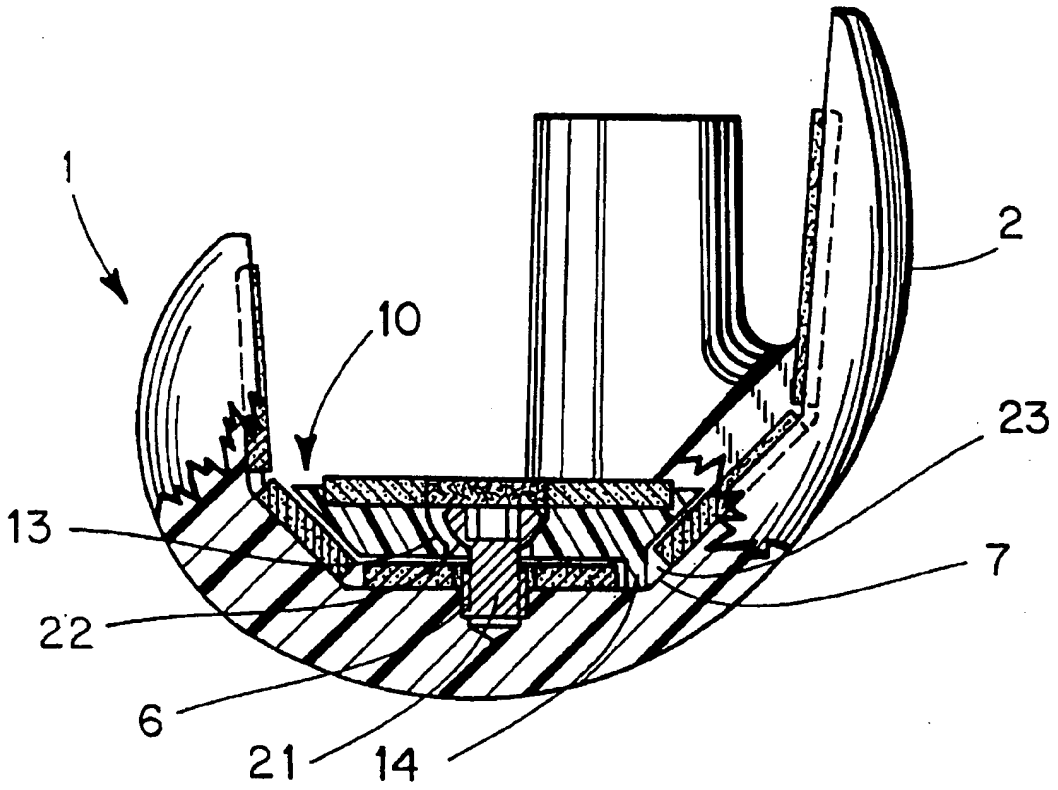
Primary Examiner—David H. Willse
Assistant Examiner—P. Zuttarelli
Attorney, Agent, or Firm—Cary R. Reeves

[57] **ABSTRACT**

An augment for an orthopaedic implant contains a countersunk through hole. A fixation means interacts with the countersink to produce both downward and lateral forces on the augment. As the fixation means is tightened, it abuts one side of the countersink so that it exerts both a downward force and a lateral force on the augment. The lateral force causes the augment to press tightly against the implant. Because of the combination of downward and lateral forces, the augment strongly resists displacement and rotation.

9 Claims, 3 Drawing Sheets



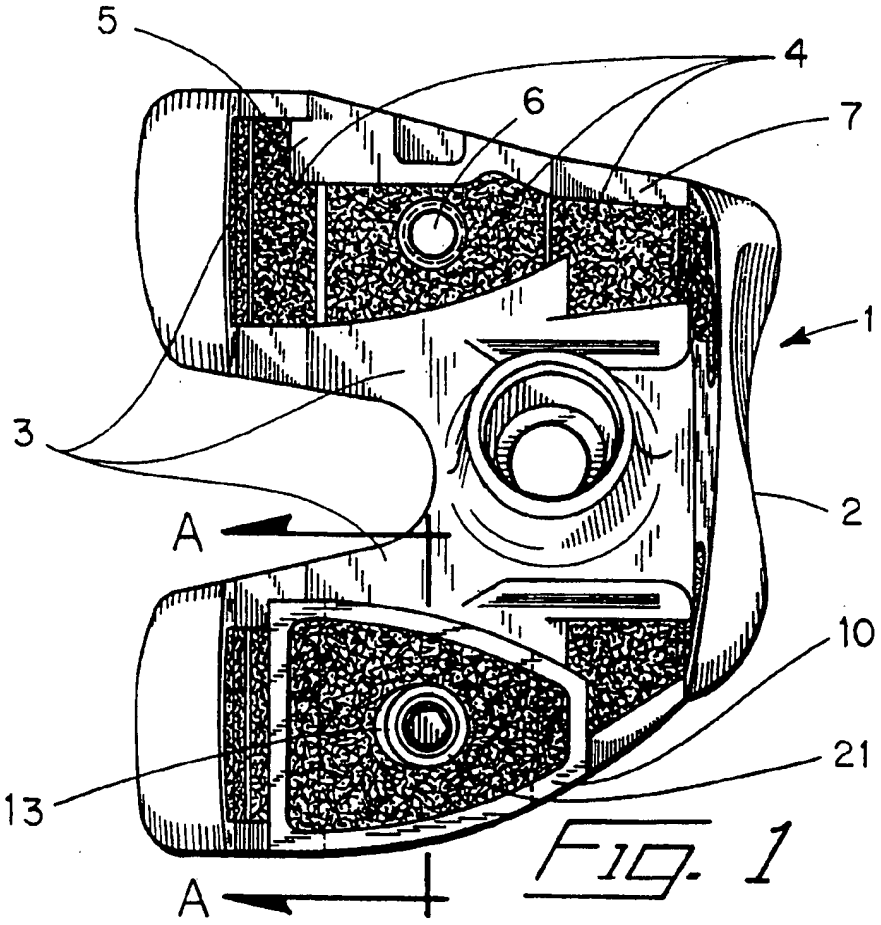


FIG. 1

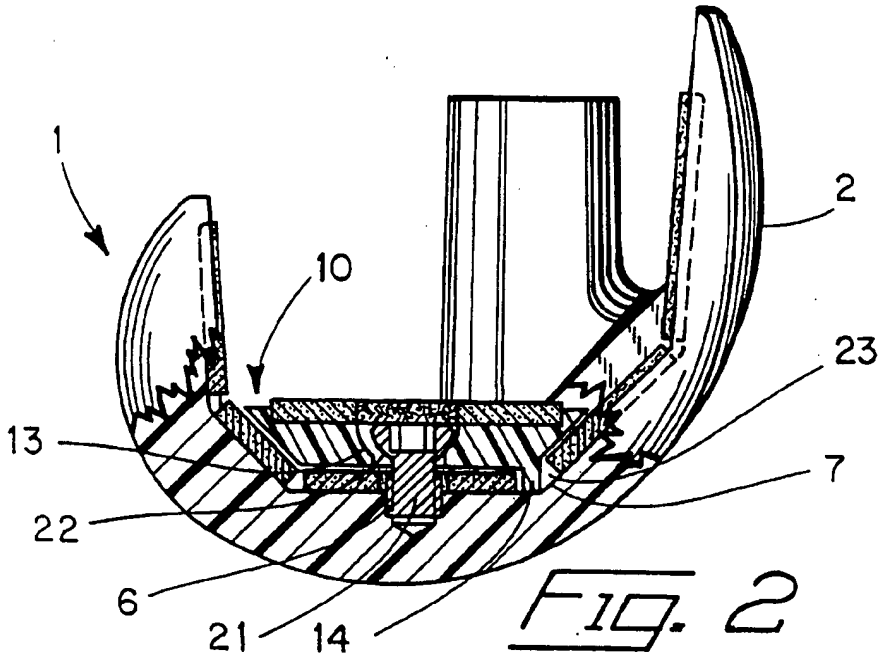


FIG. 2

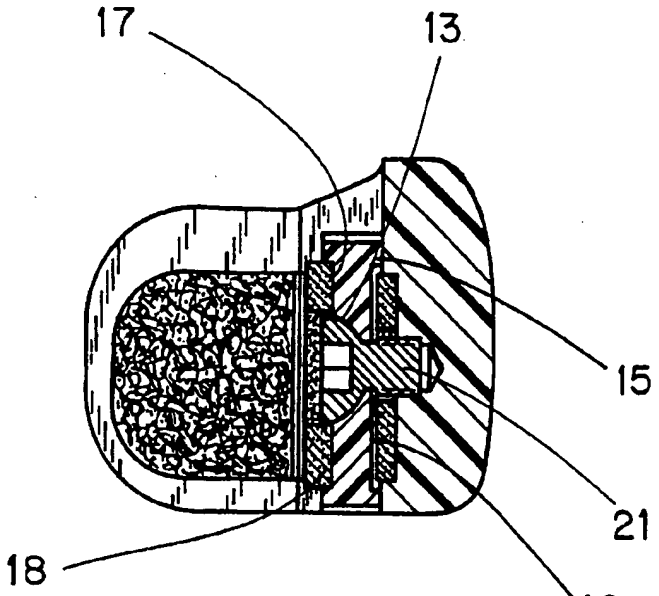


FIG. 3

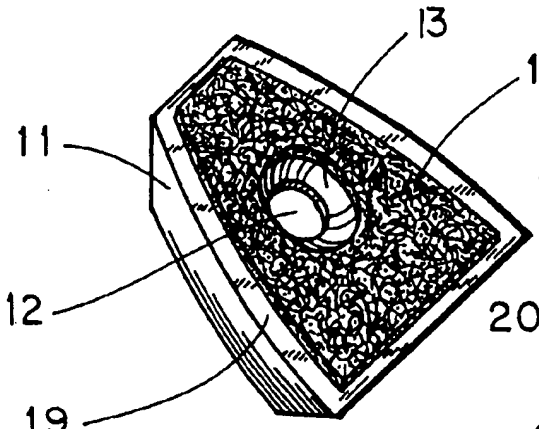


FIG. 4

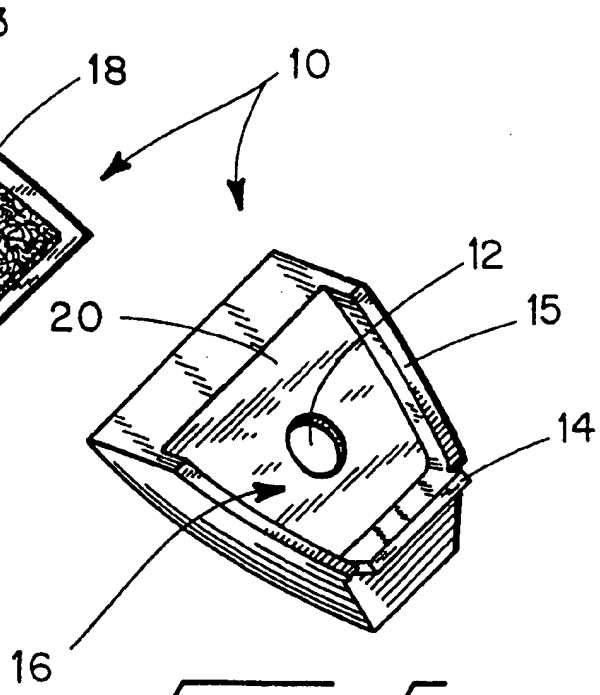


FIG. 5

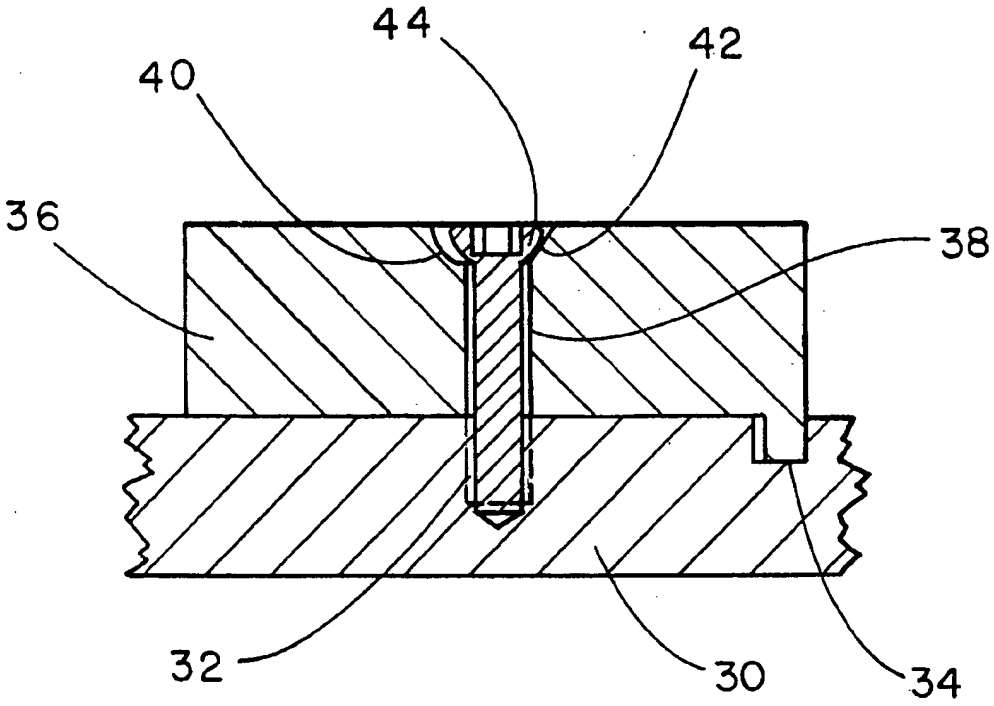


FIG. 6

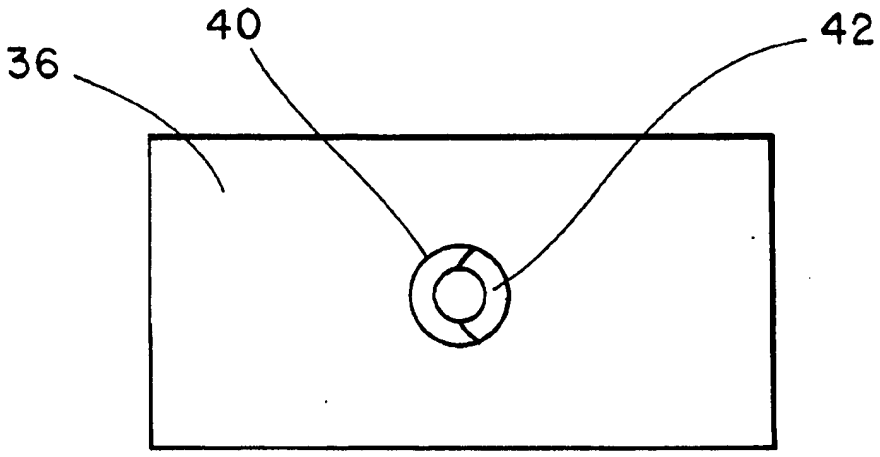


FIG. 7

AUGMENTATION FOR AN ORTHOPAEDIC IMPLANT

BACKGROUND OF THE INVENTION

This invention relates to an orthopaedic implant intended for replacing a portion of a bone. More particularly, it relates to a means for augmenting such an implant so as to adapt the implant to fit a variety of situations.

In order to replace a defective portion of a bone, such as an arthritic joint, an orthopaedic surgeon cuts away the defective portion and shapes the remaining bone to a specific geometry. An implant, having bone contacting surfaces corresponding to this specific geometry, is then placed on the bone. The implant is typically either provided with a porous surface for the bone to attach to or it is cemented onto the bone.

Implants of this type, for a particular skeletal joint, are usually made available in a range of sizes to fit the varying sizes in the patient population. However, only a relatively small number of different sizes can practically be made available. Therefore, difficulties arise when a patient has a bone of an odd size or when the bone is abnormally shaped or deformed due to disease. Often, when a bone is shaped to the specific geometry to fit an implant, only a small area of the prepared bone will exhibit a deformity such as insufficient bone to support the implant. In such cases, implant augments have been successfully used to supplement the implant and fill the bone deficiency. These augments comprise small blocks or wedges of material that can be affixed to the implant. While augments have been generally successful, the various means of attaching them to the implant have been problematic. Prior augments have been attached using screws, cements and clips.

The challenge is to provide a strong, stable attachment with a minimum number of fastening elements that are easily employed. The attachment must resist linear as well as rotational forces and large separation forces as well as smaller forces causing slight relative motion between the augment and the implant. This slight relative motion, often referred to as micro-motion is problematic in that it can lead to wear debris from the augment and implant and it can prevent the growth of a solid bony interface adjacent the augment and implant.

SUMMARY OF THE INVENTION

The present invention provides for strong, stable attachment of an augment to an implant. The attachment is resistant to large separation forces as well as micro-motion and it is resistant to linear and rotational forces. In a preferred embodiment, the augment contains a countersunk through hole. The implant is provided with a threaded hole. A screw is used to attach the augment to the implant. With the augment positioned on the implant, the center of the countersink in the augment is not aligned with the center of the hole in the implant. Therefore when the screw is placed through the augment and threaded into the implant, the screw head abuts one side of the countersink so that as the screw tightens it exerts both a downward force and a lateral force on the augment. The lateral force causes the augment to translate until it contacts a structure on the implant which resists further translation. Further tightening of the screw causes the augment to press tightly against the implant both downwardly and laterally. Because of this combination of forces, the augment strongly resists displacement and rotation. In an alternative embodiment, lateral forces are created because the countersink is asymmetric.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a plan view of the preferred embodiment of the invention.

FIG. **2** is a partially sectioned side view of the preferred embodiment of FIG. **1**.

FIG. **3** is a sectional view taken along line A—A of FIG. **1**.

FIG. **4** is an isometric view of the preferred embodiment of the augment showing the top.

FIG. **5** is another isometric view of the preferred embodiment of the augment showing the bottom.

FIG. **6** is a cross sectional view of an alternative embodiment of the invention.

FIG. **7** is a top view of the augment of the alternative embodiment of FIG. **6**.

DETAILED DESCRIPTION OF THE INVENTION

In this description, a femoral component of a knee joint prosthesis has been chosen for illustrative purposes. The component is shown with an augment attached to one side and with another side adapted for receiving an additional augment. The invention is applicable to other augmented implants in addition to femoral knee implants.

Referring to FIGS. **1–5**, an implant **1** has an articular surface **2** and an augment receiving surface **3**. In a preferred embodiment, the augment receiving surface **3** contains a pocket area **4** for receiving porous surface material **5** or other provisions such as bone cement to enhance the attachment of the implant **1** to bone. Also in the preferred embodiment, a wall **7** is formed on the implant **1** adjacent the augment receiving surface **3**. Finally, in the preferred embodiment, the implant **1** also has a threaded hole **6** in the augment receiving surface.

An augment **10** for attachment to the implant **1** comprises a body **11** having a top surface **19** and a bottom surface **20**. A through hole **12** extends through the body from the top surface to the bottom surface. A countersink **13** is formed in the top surface **19** and communicates with the through hole **12**. The preferred embodiment has a tab **14** extending from the body **11** of the augment **10** adjacent the through hole **12**. The preferred embodiment also includes side rails **15** defining a recess **16**. The preferred embodiment further includes an augment pocket **17** for receiving porous surface material **18** or other provisions such as bone cement to enhance the attachment of the augment to bone.

A screw **21** having a head with an undersurface **22** is preferably used to attach the augment **10** to the implant **1**. The through hole **12** and countersink **13** are formed so that the screw **21** exerts a lateral force as well as a downward force on the augment.

In the preferred embodiment, shown in FIGS. **1–5**, the lateral force results because the through hole and countersink are formed so that the screw **21** can pass through the augment **10** and thread into the threaded hole **6** when the center of the countersink **13** and the center of the threaded hole **6** are not in alignment. The purpose for this misalignment is so that the screw **21** can exert a lateral force on the augment **10** in addition to a downward force. In the illustrative embodiment the lateral force is directed toward the wall **7**. The hole **12** has a length corresponding to the

direction of the lateral force and a width perpendicular to the length. The countersink **13** has a similarly oriented length and width. In the preferred embodiment, the hole **12** and countersink **13** are elongated such that the length is greater than the width so that the screw fits closely along the sides, as shown in FIG. **3**, and has clearance lengthwise, as shown in FIGS. **1** and **2**.

In an alternative embodiment, shown in FIGS. **6** and **7**, the lateral force results because the countersink is asymmetric. An implant **30** has a threaded hole **32** and a translation resisting means such as slot **34**. The augment **36** has a through hole **38** and a countersink **40**. The countersink **40** is asymmetric because of the oblique surface **42**. Such an asymmetry is produced when less material is removed from a portion of the countersink or when material is added to a portion of the countersink. Because of surface **42**, a screw **44** will contact one side of the countersink even when the axes of the screw **44**, the countersink **40**, the through hole **38** and the threaded hole **32** are in alignment as shown in FIG. **6**.

In use, with respect to either the preferred embodiment or the alternative embodiment, the screw is placed through the augment and threaded into the threaded hole in the implant. The screw head abuts one side of the countersink. As the screw is tightened it exerts both a downward force and a lateral force on the augment. The augment contacts a structure on the implant, such as the wall **7** or slot **34**, which resists translation by the augment. Further tightening of the screw causes the augment to press tightly against the implant both downwardly and laterally. This combination of forces resists both linear and rotational motion of the augment relative to the implant and results in secure fixation with a single screw.

In the preferred embodiment, the side rails **15** rest on the implant **1** astride the porous surface material **18**. The recess **16** accommodates the porous surface material **18** to prevent contact between the porous surface material **18** and the augment **10**. The tab **14** extends through a gap **23** in the porous surface material **18** so that when the screw **21** is tightened the tab **14** abuts the wall **7**. In this preferred embodiment, therefore, the augment **10** is held tightly against the implant **1** and only contacts the implant **1** along the side rails **15** and the tab **14**. The tab **14** is preferably rectangular.

The preferred embodiment comprises an elongated through hole **12** in the augment and an elongated countersink **13**. However, a round countersink, one with equal length and width, would also work so long as the countersink **13**, threaded hole **6**, and translation resisting structure **7** on the implant **1** are aligned so as to produce a lateral force on the augment **10**. Likewise, the hole could be round as long as it provides enough clearance to allow the augment to press tightly against the implant. Also, in the preferred embodiment, the countersink **13** and the undersurface **22** of the screw are spherical. However, any combination of undersurface **22** and countersink surfaces that will result in a lateral force when the screw is tightened will work and the countersink and undersurface contours need not necessarily be the same, as shown in the alternative embodiment of FIGS. **6** and **7**.

The illustrated embodiments of this invention depict a screw and threaded hole for attaching the augment to the implant. Other fixation means could be used so long as they produce lateral forces in addition to downward forces. It will be understood by those skilled in the art that further variations in design and construction may be made to the preferred embodiment without departing from the spirit and scope of the invention defined by the appended claims.

What is claimed is:

1. An augment for attachment with a screw to an orthopaedic implant having a threaded hole, the augment comprising a body with a first surface and a second surface, the body having a through hole extending through the body from the first surface to the second surface and a countersink formed in the first surface communicating with the through hole, the through hole and countersink being shaped to allow the screw to pass through the through hole and thread into the threaded hole when the center of the countersink and the center of the threaded hole are not in alignment, the countersink having a spherical surface so that as the screw is tightened against the countersink surface a lateral force results tending to move the countersink into alignment with the threaded hole.

2. The augment of claim **1** wherein the through hole is elongated such that the through hole width is less than the through hole length and the countersink is elongated such that the countersink width is less than the countersink length.

3. The augment of claim **1** further including a tab extending downwardly from the second surface and perpendicular to the second surface.

4. The augment of claim **1** further including rails extending from the second surface, the rails defining a recess, the second surface forming the bottom of the recess.

5. An augmented orthopaedic prosthesis comprising:

an implant having an augment receiving surface and a threaded hole formed in the augment receiving surface;

a wall extending from the implant adjacent the augment receiving surface;

an augment comprising a body with a first surface and a second surface, the body having a through hole extending through the body from the first surface to the second surface and a countersink formed in the first surface communicating with the through hole;

a tab extending downwardly from the second surface and perpendicular to the second surface; and

a screw having a head with an undersurface, the screw engageable with the through hole and threadably engageable witch the threaded hole,

the through hole and countersink being located so that the center of the countersink and the center of the hole in the augment receiving surface are not in alignment when the augment is seated on the augment receiving surface and the tab is abutting the wall, the countersink and the undersurface being shaped so that as the screw is tightened the undersurface bears on the countersink resulting in a downward and a lateral force, the lateral force tending to move the countersink into alignment with the threaded hole and thus causing the tab to press tightly against the wall.

6. An augment for attachment to an orthopaedic implant, the augment comprising a body with a first surface and a second surface, the body having a through hole extending through the body from the first surface to the second surface and an asymmetric countersink formed in the first surface communicating with the through hole, the asymmetric countersink including an oblique surface on one side of the countersink.

7. An augmented orthopaedic implant assembly comprising:

an implant;

translation resisting means formed on the implant;

an augment having a hole extending through it, the hole including a countersink; and

fixation means cooperating with the countersink to produce both downward and lateral forces on the augment,

the lateral force pressing the augment against the translation resisting means.

8. The implant assembly of claim 7 wherein the translation resisting means is a slot formed in a surface of the implant and the augment includes a tab extending downwardly from the augment, the tab and slot being in engagement so as to resist translation of the augment relative to the implant.

9. An augment for attachment with fixation means to an orthopaedic implant, the augment comprising a body having a hole extending through it, the hole including a countersink, the fixation means cooperating with the countersink to produce both downward and lateral forces on the augment, the lateral force pressing the augment against the implant.

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United States Patent [19]

Li et al.

[11] Patent Number: 5,263,984

[45] Date of Patent: Nov. 23, 1993

[54] PROSTHETIC LIGAMENTS

[75] Inventors: **Shu-Tung Li**, Oakland, N.J.; **Kevin R. Stone**, Mill Valley, Calif.

[73] Assignee: **ReGen Biologics, Inc.**, San Francisco, Calif.

[21] Appl. No.: **872,636**

[22] Filed: **Apr. 22, 1992**

Related U.S. Application Data

[60] Continuation-in-part of Ser. No. 582,516, Sep. 13, 1990, Pat. No. 5,116,374, which is a division of Ser. No. 317,951, Mar. 2, 1989, Pat. No. 5,007,934, which is a continuation-in-part of Ser. No. 75,352, Jul. 20, 1987, Pat. No. 4,880,429.

[51] **Int. Cl.**[5] **A61F 2/08**

[52] **U.S. Cl.** **623/15**; 623/66

[58] **Field of Search** 623/1, 2, 11, 12, 15, 623/17, 16, 18, 20, 66; 128/DIG. 8

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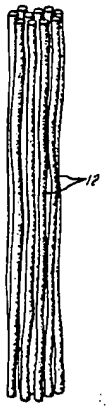
Primary Examiner—David Isabella
Attorney, Agent, or Firm—Lahive & Cockfield

[57] **ABSTRACT**

Disclosed is a prosthetic ligament comprising a Plurality of substantially aligned, elongated filaments. Each filament is a dry, porous, volume matrix of biocompatible and bioresorbable fibrils, at least some of which are crosslinked. The fibrils are short segments of longer fibers of polymeric connective tissue components, or analogs thereof. Each filament establishes a bioresorbable scaffold adapted for ingrowth of ligament fibroblasts, the scaffold and the ingrown fibroblasts supporting natural ligament tensile forces. Also disclosed are methods of fabricating the prosthetic ligament, and methods of regenerating ligamentous tissue in vivo.

21 Claims, 4 Drawing Sheets



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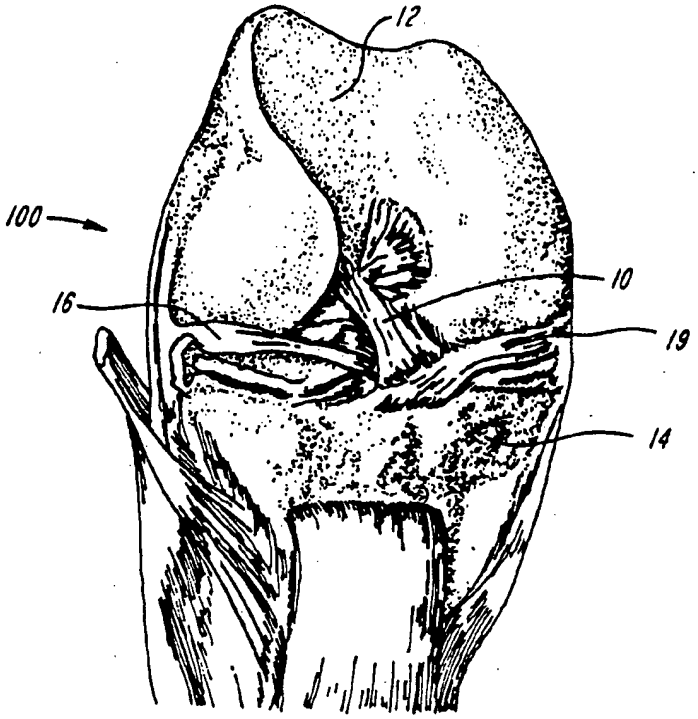

FIG. 1A

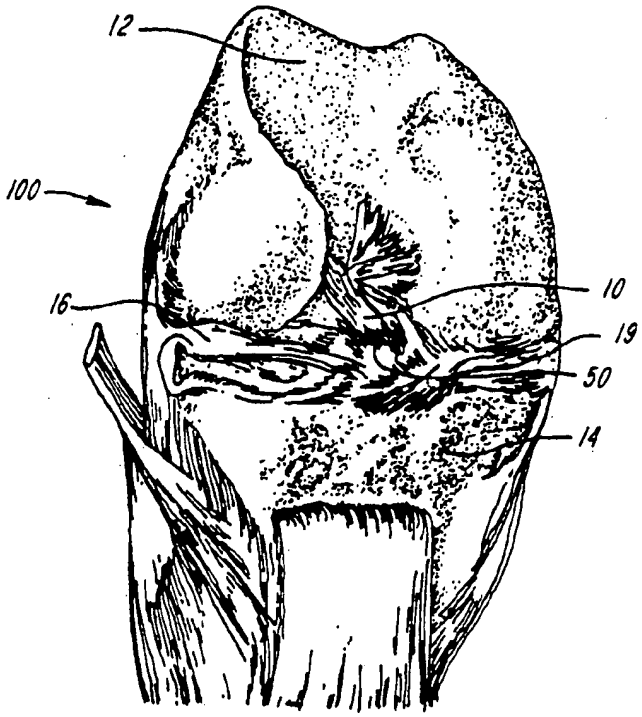

FIG. 1B

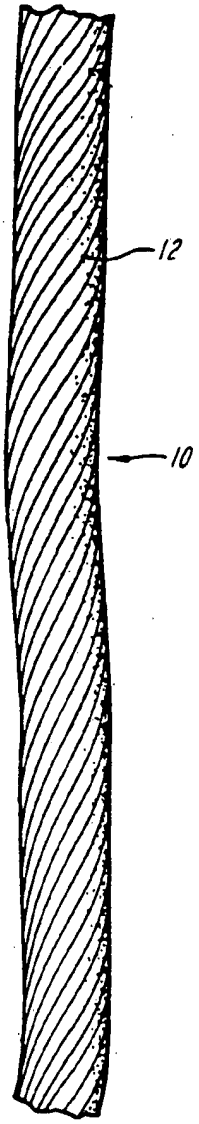

FIG. 2C

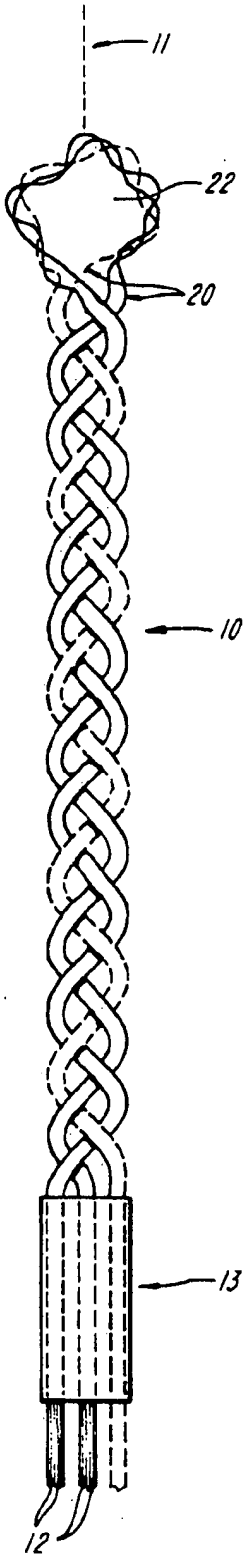

FIG. 2A

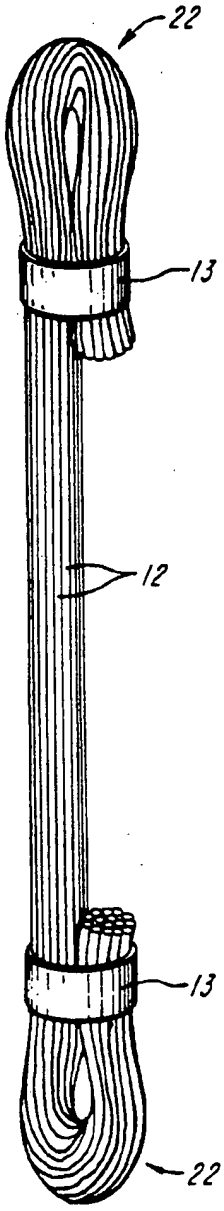

FIG. 2E

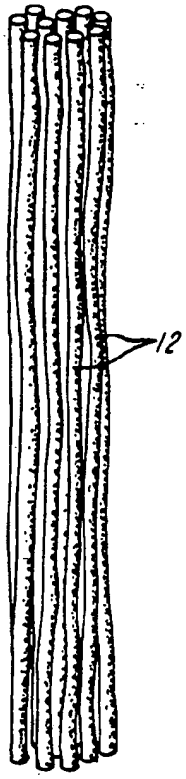

FIG. 2D

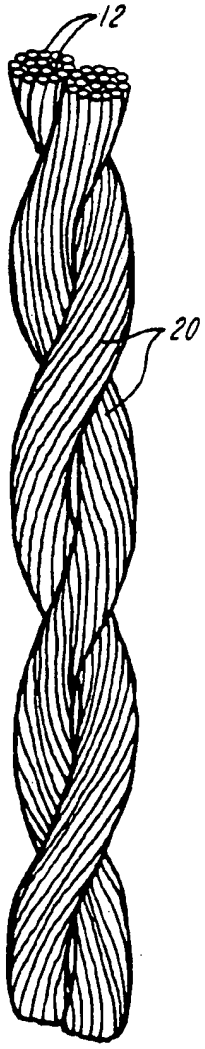

FIG. 2B

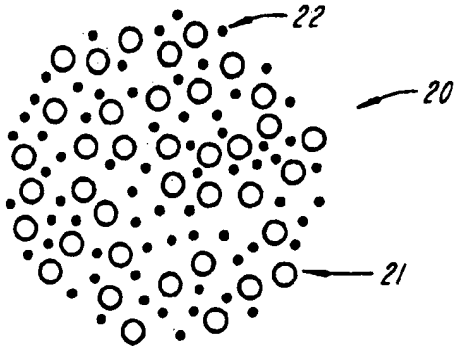

FIG. 3

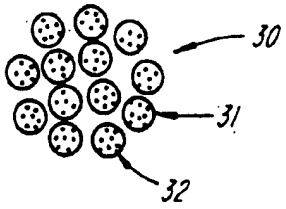

FIG. 4

FIG. 5

PROSTHETIC LIGAMENTS

REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of copending U.S. patent application Ser. No. 582,516 filed Sep. 13, 1990, now U.S. Pat. No. 5,116,374, which is a divisional of U.S. patent application Ser. No. 317,951, filed Mar. 2, 1989, now U.S. Pat. No. 5,007,934, issued Apr. 16, 1991, which is a continuation-in-part of U.S. patent application Ser. No. 075,352, filed Jul. 20, 1987, now U.S. Pat. No. 4,880,429, issued Nov. 14, 1989.

BACKGROUND OF THE INVENTION

The present invention is in the field of implantable medical devices and prostheses. More particularly, this invention is directed to devices useful as prosthetic ligaments and in vivo scaffolds for the regeneration of ligamentous tissue, and to methods of their fabrication and use.

Ligaments connect one bone to another usually where the bones form articulating joints in the human and animal species. The ligaments act in the joint as a mechanism for maintenance of joint stability, for guidance of joint motion, and for resistance to joint distraction forces. Without ligaments, the human and animal species would be unable to maintain the erect form. Injury to the ligaments results in either a normal physiological repair process, which can lead to resumption of normal joint mechanics, or to inadequate repair with loss of joint stability, abnormal joint motions, and occasionally to painful arthritis as a result of abnormal joint surface wear and tear. In general, ligaments that are outside of joints, and bathed in a rich vascular supply, have a good chance of healing normally after injury. Ligaments that are inside of joints, termed intra-articular ligaments, are generally bathed in synovial fluid, have a relatively poor blood supply, and heal poorly.

In the prior art, treatment of injured ligaments has generally been both by attempts to protect the ligament from further deforming stress and thereby to permit a normal physiological repair process to occur or to attempt a surgical repair with sutures, replacement, or excision (Johnson, R. J. et al. (1992) *J. Bone Joint Surg.* 74-A:140-151; Arnold et al. (1979) *Am. J. Sports Med.* 7:305; McDaniel et al. (1983) *Clin. Orthop.* 172:158; Rovere et al. (1983) *Am. J. Sports Med.* 104:205). With non-operative or operative repair, healing and regeneration of ligamentous tissue may occur. Generally, if the ligament is located intra-articularly, the repaired tissue is usually inferior to the original tissue and sometimes inadequate to withstand the normal joint forces. In view of the insufficiency of many primary repairs several previous attempts have been made to replace the ligamentous tissue with natural and artificial materials. Unfortunately, this also has resulted in significant problems related to those replacement materials.

In particular, replacement of ligaments in the prior art has been by autografting (Friedman et al. (1985) *Clin. Orthop.* 196:9), allografting (Webster (1983) *Clin. Orthop.* 181:238), xenografting (McMaster (1988) in "*Prosthetic Ligament Reconstruction of the Knee*" (Friedman and Ferkel, (eds.), W. B. Saunders, Philadelphia, pp. 96-100), or by using synthetic materials (Woods (1985) *Orthop. Clin. North Am.* 16:227). Autografting, or the substitution of the injured ligament with ones own tissue, is still the preferred modality (Amiel et al. (1986) *Am. J. Sports Med.* 14:449-462; Warren et al. (1990) *AAOS 57th Annual Meeting,* Anaheim, Calif, p. 84). Autografting alleviates the risk of transmission of diseases between donor and recipient, immunological complications, and complications from foreign body reactions. However, the weakening of the body part from which the substitution tissue is harvested, the extensive surgical procedures with both harvesting of the donor tissue and substituting the injured tissue, and the inadequate mechanical strength of the substituted tissues have prompted the search for alternative methods of repair.

Allografting, or the substitution of injured ligament with tissues from another person (either preserved live tissue or chemically processed tissue), has been practiced (Noyes et al. (1990) *J. Bone Joint Surg.* 72-A:1125-1136; Shine et al. (1990) *Am. Sports Med.* 18:457-465; Webster (1983) *Clin. Orthop.* 181:238; Bright et al. (1981) *J. Pediatr. Orthop.* 1:13). This approach has been only partially successful over the long term due primarily to the host's immunologic response to the graft, and to failures in the preservation and sterilization processes (Jackson et al. (1990) *Am. J. Sports Med.* 18:1-10; Minami et al. (1982) *Hand* 14:111). In addition, the risk of disease transmission is of particular concern for allografting (Prewett et al. (1991) *Orthop. Res. Soc.* 16:456).

Xenografting, or the substitution of the injured ligament with tissues from animal sources, has been tried. However, because of inadequate material processing leading to the presence of toxic and immunological substances in the graft, this method has met with minimal success (Teitge (1988) in *The Crucial Ligament,* (Feagin, ed.) New York, Churchill-Livingston, pp. 529-534).

Various synthetic polymers have been fabricated for ligament substitution, such as polypropylene, polyethylene terephthalate, carbon, polytetrafluroethylene (Claes et al. (1991) *Orthop. Res. Soc.* 16:598). Ligament substitution devices are intended to function as permanent implants, and thus are subjected to continuous intraarticular wear and tear. However, none of the present synthetic polymeric ligament devices has functioned successfully as a ligament substitute. Such devices have failed because of ligament rupture, joint particle reduction and resultant synovitis, abrasion of opposing joint surfaces, infection required extensive joint debridement and ligament removal, persistent effusion, and bony tunnel widening (Woods et al. (1991) *Am. J. Sports Med.* 19:48-55; Woods (1985) *Orthop. Clin. North Am.* 16:227). Thus, artificial materials are generally insufficiently durable or mechanically compatible to tolerate the repetitive joint loading, and have never been demonstrated to restore normal joint mechanics.

The concept of a resorbable template or scaffold for tissue repair and regeneration has received rigorous attention in recent years. Repair of tissues such as skin, nerve, and meniscus has been attempted using both the synthetic and natural resorbable polymers. For example, Yannas et al. (U.S. Pat. No. 4,060,081) fashioned endodermal implants out of glycosaminoglycans and natural collagen. Nyiles et al. (*Trans. Am. Soc. Artif. Intern. Organs* (1983) 29:307-312) reported the use of synthetic resorbable polyesters for peripheral nerve regeneration applications. Li (U.S. Pat. No. 4,963,146) used a porous, semipermeable, resorbable collagen conduit as a scaffold for nerve regeneration.

However, even with the foregoing technologies, which have been applied to the reconstruction of anatomical structures, a structure successful as a prosthetic ligament and constructed from totally resorbable materials, or analogs thereof, has not yet been developed. Therefore, what is needed is a prosthetic ligament including a scaffold composed of biocompatible materials which is soft, strong, resorbable, and which can support ligamentous growth.

Accordingly, it is an object of this invention to provide a ligament replacement or prosthesis which is biomechanically able to withstand normal joint forces and is able to function at those loads to protect the surrounding cartilage.

Another object is to provide a ligament replacement or prosthesis which is biomechanically able to provide joint stability.

Yet another object is to provide a resorbable prosthesis which acts as temporary in vivo scaffold for ligament fibroblast infiltration and ligament regeneration.

A further object is to provide a method for insertion and fixation of a ligament prosthesis.

Another object is to provide a method of regenerating ligamentous tissue in vivo.

Still a further object is to provide a method by which such prosthetic ligament can be fabricated.

SUMMARY OF THE INVENTION

The present invention provides a biocompatible and bioresorbable structure for implantation adjacent and into articulating joints which assumes the form and role of the ligament. This prosthetic ligament promotes and provides a scaffold for the regeneration of tissue having the physical characteristics of natural ligament tissue whereby the scaffold and the ingrown fibroblasts support natural ligament tensile forces.

The prosthetic ligament of the invention is a plurality of substantially aligned, elongated filaments substantially aligned in a mutually adjacent relationship. These filaments establish a bioresorbable scaffold adapted for ingrowth of ligament fibroblasts, and together with those ingrown cells, support natural ligament tensile forces.

Each filament is a dry, porous, volume matrix of biocompatible and bioresorbable fibrils, at least some of which are crosslinked. "Fibrils" as used herein are segments or short pieces of fibers of native polymeric connective tissue-type components, such as those obtained from human, animal tissues, plants, insects, or analogs thereof. Preferable connective tissue-type components include collagen, elastin, reticulin, cellulose, alginic acid, and chitosan, with the most preferable being collagen type I.

Some of the fibrils in the filament are connected via intramolecular and/or interfibrillar crosslinks. In one aspect of the invention, these crosslinks are formed by a chemical crosslinking reagent such as one selected from the group consisting of glutaraldehyde, formaldehyde, carbodiimides, hexamethylene diisocyanate, bisimidates, glyoxal, polyglycerol polyglycidyl ether and adipyl chloride. A preferred chemical agent is formaldehyde.

In some embodiments of the invention, the fibrils are randomly oriented throughout the matrix. In other forms, these fibrils are predominantly oriented along the axis of the filament.

A preferred prosthetic ligament also includes polysaccharide molecules interspersed with the fibrils. In various forms of the invention, these polysaccharides directly participate in covalent crosslinking formation with the fibrils, or interact with the fibrils mechanically in the form of entanglement or through interlocking mechanism, forming stable fibril-polysaccharide complexes. As such, these polysaccharides molecules provide lubrication, hydrophilicity, and strength to the prosthetic ligament. Preferably, these polysaccharide molecules have a molecular weight greater than 1000, and are selected from the group consisting of chondroitin 4-sulfate, chondroitin 6-sulfate, keratan, dermatan sulfate, haparan sulfate, heparin, hyaluronic acid, alginic acid, chitosan, cellulose, and mixtures thereof. These polysaccharides may be uniformly dispersed throughout the prosthetic ligament as individual molecules, or may be present in varying amounts in different regions of the structure.

The matrix includes about 75 to 100% natural and/or synthetic fibers and about 0 to 25% polysaccharide molecules by dry weight, the proportions of which may be constant throughout the structure or may be variable.

In one preferred embodiment of the invention, the prosthetic ligament is primarily a composite of two densities of filaments, with the more porous, or "low density" filament having a density of from about 0.05 to 0.4 g matrix/cm^3, and more preferable, from about 0.07 to 0.3 g matrix/cm^3, (where "g matrix/cm^3" is a unit connoting the number of grams in a cubic centimeter of the matrix), and the less porous, or "high density" filament has a density in the range of from about 1.0 to about 1.3 g matrix/cm^3.

In one embodiment, the prosthetic ligament has the shape of a filamentous braid with a loop at one end and a straight bundles of filaments at the other end to aid in insertion and fixation to bone. In another, a plurality of filaments are twisted together.

In yet another embodiment of the invention, the prosthetic ligament further comprises a mesh or membrane composed of a bioresorbable, biocompatible material which is attached to portions of the outer surface of the matrix. The mesh or membrane aids in the implantation of the prosthetic ligament into the joint by providing a temporary anchoring mechanism.

This invention also encompasses a method of fabricating a prosthetic ligament of the type described above. Generally, the method includes the following steps. A plurality of essentially pure fibers of a polymeric connective tissue component is provided and cut into a plurality of segments or fibrils which are shorter than the fibers. Cutting may be accomplished by mechanical disintegration, for example. The fibrils are then aggregated into a plurality of elongated filaments and contacted with a crosslinking reagent for a time sufficient to crosslink at least a portion of the fibrils within the filaments. The filaments are then aligned in a mutually adjacent relationship to form the prosthetic ligament. Polysaccharide molecules may be added to the fibrils before the aggregation step to form polysaccharide-containing prosthetic ligaments.

In one embodiment of the invention, the aggregation step is accomplished by providing a dispersion of fibrils; forming the dispersion into a filamentous shape; and drying it to form a filament. The forming step can include extruding the dispersion from a syringe into a coacervation bath of a high concentration neutral salt. Alternatively, the dispersion is placed into a mold form having a filamentous shape such that the fibrils are ran-

domly or uniformly oriented throughout said dispersion in said mold form. Portions of the coacervated fibrils are freeze-dried to produce the low density filaments, and other portions are air dried to obtain the high density filaments. Both the low and high density filaments are crosslinked to increase the strength and in vivo stability of the prosthetic device.

In a preferred aspect of the invention, the crosslinking step is performed using chemical crosslinking reagents which form interfibrillar and intermolecular crosslinks. In other aspects of the invention, an additional crosslinking step is performed by subjecting the chemically crosslinked matrix to a dehydrothermal crosslinking procedure with heat and vacuum.

Further, the invention includes a method of regenerating ligamentous tissue in vivo. This method includes providing the prosthetic ligament of the invention and implanting it into a joint by known surgical procedures.

The invention will next be described in connection with certain illustrated embodiments. However, it should be clear that various modifications, additions, and deletions can be made without departing from the spirit or scope of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

The foregoing and other objects of this invention, the various features thereof, as well as the invention itself, may be more fully understood from the following description, when read together with the accompanying drawings in which:

FIGS. 1A and 1B are diagrammatic representations of a human knee joint showing the normal positioning of the articular ligaments (FIG. 1A); and an articular ligament injury (FIG. 2B);

FIGS. 2A-2E are a perspective views of exemplary prosthetic ligaments in accordance with the present invention;

FIGS. 3 is a perspective sectional view of the prosthetic ligament of FIG. 2A;

FIG. 4 is a perspective sectional view of a low density filaments of the present invention; and

FIG. 5 is a sectional view of high density filaments of the present invention.

DESCRIPTION OF THE INVENTION

Ligament fibroblasts have the ability to regenerate ligamentous tissue if given the right physical and chemical environment in which to do so (Frank et al. (1983) *J. Orthopaed. Res.* 1:179-188). Additionally, ligament fibroblasts can migrate into a defect filled with a fibrin clot and form tissue apparently similar to ligament (Frank et al. (1983) *J. Sports Med.* 11:379-389). When an adequate matrix scaffold is present within a ligamentous defect, such ligamentous tissue may be formed. Full regeneration of an injured ligament in an otherwise healthy joint may provide normal joint motion and stability thereby preventing arthritic changes.

It has been discovered that a prosthetic ligament fabricated from short segments of fibers of biocompatible and bioresorbable polymeric connective tissue components can be surgically implanted into the knee, shoulder, or other joint so as to provide normal joint motion and stability. This prosthetic ligament also acts as a scaffold for regenerating ligamentous tissue whose ingrowth is encouraged by the physical characteristics of the implanted device.

FIG. 1A shows a diagrammatic representation of the normal positioning of a native anterior cruciate ligament **10** in the human knee joint **100**. This ligament connects femur **12** to tibia **14** between lateral meniscus **16** and medial meniscus **19**. The prosthetic ligament of the present invention can be used to replace or enhance the functioning of such a native ligament. FIG. 1B shows a typical articular ligament injury **50** that the prosthetic ligament of the invention could be used to repair.

An exemplary prosthetic ligament **10** is shown in FIG. 2A. The prosthetic ligament **10** is generally a plurality of substantially aligned, elongated filaments **12** which extends along a central axis **11**. In this embodiment, the filaments **12** have been braided or woven together about the axis **11**. Brace or tube **13** holds filaments **12** together. In an alternative embodiment shown in FIG. 2C, filaments **12** have been twisted together, forming a rope-like structure. Other types of structures which include filaments aligned in a mutually adjacent relationship are also useful (FIGS. 2B, 2D, and 2E).

The prosthetic ligament may be fabricated from of any biocompatible, bioresorbable fibers of a native, synthetic, or biosynthetic polymeric connective tissue or plant connective tissue-like component. Examples of such materials include collagen, reticulin, elastin, cellulose, alginic acid, and chitosan. The following procedure may be used to prepare the type I collagen from bovine Achilles tendon.

Tendon is first cleaned of fascia and extraneous tissues and minced. The minced tendon is extracted in a 1M NaCl, pH 7.0, to remove a small portion of the collagen molecules that are newly synthesized and have not yet been incorporated into the stable fibrils, as well as glycoproteins and proteoglycans that are associated with collagen through non-covalent interactions. Other salts such as potassium chloride and the like can be used as a substitute for sodium chloride.

Lipids that are associated with the cell membranes or collagenous tissues are removed by first extracting with detergents such as Triton X-100 (Sigma Chemical Co., St. Louis, Mo.), followed by extracting with ether-ethanol mixtures. The concentration of Triton X-100 is usually about 2% to 4%, but is preferably about 3%. The preferred mixture of ether-ethanol is usually at about a 1:1 ratio (v/v). The period of extraction is usually from about 8 hours to about 96 hours, but is preferably from about 24 to 48 hours.

Further purification may be accomplished by extracting the tendon under acidic and basic conditions. Both acidic and basic extraction weaken the non-covalent intermolecular interactions, thus facilitating the release of non-covalently attached glycoproteins, glycosaminoglycans (GAGs), and other non-collagenous molecules.

The extraction of tendon at alkaline condition is accomplished by treating the tendon with $Ca(OH)_2$, NaOH, or the like, at a pH about 13 for a period of 8 to 96 hours in the presence of a structure-stabilizing salt such as $(NH_4)_2SO_4$, or Na_2SO_4 to minimize the potential risk of denaturating the collagen. Alkali treatment dissociates the non-covalently-linked glycoproteins and GAGs from the collagen matrices. The alkali also removes the residual lipid through saponification.

The acid extraction may be conducted at a PH below 3 in the presence of a structure stabilizing salt. Acids such as acetic acid, hydrochloric acid, or the like may be used. Like alkaline extraction, acid extraction removes non-covalently-linked glycoproteins and GAGs.

The non-triple helical portions of the molecule (telopeptides) are involved in intermolecular crosslinking formation. They are weak antigens and are susceptible to attack by proteases, such as pepsin and trypsin. Prolonged digestion with such proteases dissociates the fibrils into individual molecules. However, if the digestion process is properly controlled such that maximal telopeptides are removed without complete dissociation, the immunogenicity of the fibrils may be further reduced without significantly comprising the mechanical strength. For example, to isolate molecular collagen, the digestion of skin or tendon with pepsin is usually conducted at an enzyme:collagen ratio of about 1:10 (w/w) for about 24 to 96 hours at below room temperature. In comparison, fibrils may be obtained by limited pepsin digestion achieved at a ratio of about 1:100 (enzyme:collagen w/w) for about 24 to 96 hours at 4° C.

Type I collagen fibrils obtained according to this method are used to fabricate the prosthetic ligament of the present invention. However, it must be appreciated that collagen obtained from other sources, such as biosynthetically-produced collagen or analogs thereof, may also be used in the fabrication of the prosthetic ligament. These fibers may be ordered in substantially longitudinally-extending with the density of fibers being substantially uniform throughout the matrix.

The following general procedure may be used to fabricate a prosthetic ligament.

The purified connective tissue fibers are swollen in a phosphate buffered saline solution at pH 7.4. The swollen fibers are then subjected to a homogenization step to further break down the fibers to smaller fibrils without denaturing the protein. Homogenization under low shear rate is preferred, such as with a Silverson Homogenizer adapted with a disintegration head. The homogenized connective tissue is then filtered first through a 40 mesh then through a 100 mesh stainless steel screen to eliminate large fibers that have not been homogenized. The uniformly dispersed connective tissue fibrils can now be used for the production of high density and low density filaments.

One method of forming a filament includes an extrusion procedure. Briefly, a collagen or other fibril dispersion (2% to 4% w/v) is fed into a reservoir which is attached to a piston-driven device on one side and a needle at the other end such as a syringe pump device. The dispersion is pushed out through the needle through a continuous, constant piston drive to ensure a continuous, constant flow of the dispersion. The wet filaments may be extruded into a coacervation bath of acetate buffer solution, pH 4.7, in the presence of 1% NaCl. Alternatively, the wet filaments may be extruded into a salt solution bath containing 5 to 20% NaCl.

Another method of forming a filament includes placing or aggregating the dispersion into a mold form having a filamentous shape. The fibrils in the dispersion may randomly or uniformly orientated in the mold, depending on the application desired. Uniform orientation in the mold may be accomplished for example by directionally painting the dispersion into the mold with a bristled brush.

The prosthetic ligament contains porous low density filaments, and may also contain high density filaments for added strength. A typical prosthetic ligament consists of from about 10% to about 50% low density filaments having density of from about 0.05 to about 0.4 g/cm^3, and preferably about 0.07 to about 0.3 g/cm^3, and from about 50% to about 90% high density filaments having density from about 1.0 to about 1.3 g/cm^3.

To form low density filaments, the wet filaments are removed from the coacervation bath and freeze-dried. These freeze-dried filaments are highly porous and do not possess high tensile strength. The porosity and strength are adjusted by stretching the filaments and then subjecting the filaments to a crosslinking agent. Vapor crosslinking with formaldehyde is preferred. Alternatively, the stretched filaments may be crosslinked by dehydrothermal treatment with heat and vacuum by methods well known in the art.

High density filaments are obtained as follows. Filaments are extruded from a dispersion (2 to 4% w/v) as described above. However, after the wet filaments are collected, they are air dried under a hood to yield collagen filaments of a given diameter. The air dried filaments are subsequently crosslinked either in a solution phase using a crosslinking agent well known in the art such as glutaraldehyde, formaldehyde, and the like, or in a vapor phase also known in the art such as by exposing the filaments to formaldehyde vapor.

The filaments are then manipulated into a desired shape such as a multi-filament bundle **20** which then can be used to form a multi-filament braid of three or more bundles **20** of high density and/or low density filaments **12** (FIG. **2A**), a two or more bundle helix (FIG. **2B**), or a single twisted bundle (FIG. **2C**) or untwisted bundle (FIG. **2D**). FIG. **2E** shows an embodiment **20** similar to that shown in FIG. **2D** where loops **22** are formed at each end for use in fastening the prosthetic ligament in vivo.

The following procedure may be used to prepare a ligament device of braided filaments, as shown in FIG. **2A**. High density and low density filaments at a ratio of 2:1 (w/w) are combined longitudinally in small bundles, having about 100 to 300 high density filaments and 50 to 150 low density filaments. Three bundles are first braided at the mid-length and then folded at the braided region to form a turn and a loop **22**. The six bundles are then braided. The end of the ligament is sealed into a resorbable polymer mesh tube **13** such as a polylactate mesh tube. The thusly braided ligament can easily be stretched by 10 to 15% without strain the collagen molecules.

The crosslinked device maintains sufficient degree of hydrophilicity and elasticity which simulates the properties of the natural ligament, i.e., ability to sustain mechanical stress and to stabilize the joint. In addition, the structure provides an ideal environment for cell infiltration, extracellular matrix synthesis, and deposition resulting in regeneration of natural ligament tissue.

Polysaccharides may be dispersed throughout the fibrils in the filaments. They may act as lubricants and/or intermolecular crosslinks between fibrils. Useful polysaccharides crosslinks are composed typically of at least one of the group of molecules consisting of chondroitin 4-sulfate, chondroitin 6-sulfate, keratan sulfate, dermatan sulfate, heparan sulfate, heparin sulfate, alginic acid, chitosan and hyaluronic acid. The dispersion of polysaccharides is preferably uniform throughout the fibril dispersion and may be in the range of about 1 to 25% (weight/weight) for example.

Intermolecular crosslinkages can also be established through a dehydrothermal process (heat and vacuum) which is well known in the art. This procedure can be performed as an additional step after chemical crosslinking for added strength.

The crosslinked device has a relatively high thermal stability between about 55° to 85° C., preferably between about 65° to 75° C., for sufficient in vivo stability. This may be achieved through manipulation of the crosslinking conditions, including reagent concentration, temperature, pH and time.

By following the processes described above and in the examples set forth below, a prosthetic ligament of the forms shown in FIG. 2 may be constructed having the characteristics listed below in TABLE 1.

TABLE 1

1. Physical Characteristics	
a. Density (g/cm^3)	
low density filaments	0.05–0.4
high density filaments	1.0–1.3
b. Tensile Strength (Newtons)	
initial	300–600
after tissue ingrowth	1000–3000
c. Length (cm)	15–17
2. Constituents	
a. Fibers	
type I or type I + type II collagen, (weight %)	75–100
b. Polysaccharides (weight %)	0–25

The following non-limiting examples describe methods of fabrication and in vivo testing of the prosthetic ligament of the invention.

EXAMPLE 1

Preparation of Purified Type I Collagen

A) Tissue

Bovine, porcine or sheep Achilles tendon is obtained from USDA-approved slaughter houses. The preferred age of the animals is between 12 to 18 months. The tissue is kept cold during the purification process except where specified to minimize bacteria contamination and tissue degradation.

B) Mechanical Disintegration

The adhering tissues of carefully selected tendons are first scrapped off mechanically. The tendons are then minced or cut into fine pieces and washed in excess quantities (10 volumes) of cold water to remove residual blood proteins and water soluble materials.

C) Salt Extraction

The washed tendons are extracted in ten volumes of 5% NaCl, 0.1M phosphate buffer, pH 7.4 for 24 hours to remove salt soluble materials. The salt extracted tendons are repeatedly washed in about 10 volumes of water to remove the salt.

D) Lipid Extraction

The material is extracted in 3% Triton X-100 for 24 hours. The detergent is removed by extensive washing with water. The material is then extracted in 3 to 4 volumes of ether-ethanol (1:1 vol/vol) for 24 (±2) hours to further minimize the lipid content. The lipid extracted material is extensively washed in water to remove the ether and ethanol.

E) Acid and Base Extraction

The material is subjected to acidic and basic extractions to remove non-collagenous materials. Alkaline extraction is conducted with 3 to 4 volumes of 0.5M NaOH at pH 13 to 13.8 at room temperature in the presence of 1.0M Na_2SO_4 for 24 (±2) hours with mild agitation. Following alkaline extraction, the pH is neutralized with HCl. The pH is then adjusted to 2.5 by adding concentrated lactic acid to a final concentration of 0.2M. The acid extraction is continued for 24 (±2) hours with agitation.

F) Limited Proteolytic Digestion

The acid swollen tendon is then subjected to a limited proteolytic digestion with pepsin (enzyme:collagen=1:100 w/w) for 24 (±2) hours at 4° C. The pepsin and telopeptides are removed through dialysis.

The swollen fibrillar material is then coacervated by adjusting the pH to its isoionic point with 1M NaOH or HCl or by adjusting the ionic strength to 0.7 with NaCl. The coacervated collagen fibrils are harvested by filtration, and the filtered material extensively washed with cold distilled water. The highly purified type I collagen may be stored at −20° to −40° C. until use. Alternatively, the purified fibril dispersion may be freeze dried and stored at room temperature as dry fibrils.

EXAMPLE 2

Preparation of Low Density Filaments

15 grams of purified collagen fibrils are swollen in 500 ml phosphate buffered saline (PBS) solution to make a 3% (w/v) collagen dispersion. The swollen collagen is homogenized with a Silverson Homogenizer using a disintegration head for two minutes. The homogenized collagen is then filtered first through 40 mesh stainless steel mesh followed with a 100 mesh stainless steel filtration under vacuum. The filtered, dispersed collagen is de-aired under vacuum. The uniform collagen dispersion is fed into a syringe pump which extrudes the collagen through a modified 12 gauge needle at a rate of 1 ml per minute. The extruded collagen filaments are collected in a coacervation tank of acetate buffer pH 4.7 in the presence of 1% NaCl at 35° C. The coacervated filaments are then placed into freeze drying trays and frozen at −40° C. followed by drying at −10° C. under 150 um Hg vacuum for 24 hours. The final drying is done at 20° C. for six hours before removing the filaments from the freeze drying trays. The freeze dried collagen filaments are placed in a crosslinking chamber and crosslinked under vapor of formaldehyde generated from a 2% formaldehyde solution for 90 minutes at 95% humidity at room temperature. The crosslinked collagen filaments are stored at room temperature in a clean plastic bag until further use.

EXAMPLE 3

Preparation of High Density Filaments

15 grams of purified collagen fibrils are swollen in 500 ml phosphate buffered saline (PBS) solution to make a 3% (w/v) of collagen. The swollen collagen is homogenized with a Silverson Homogenizer using a disintegration head for two minutes. The homogenized collagen is then filtered first through 40 mesh stainless steel mesh followed with a 100 mesh stainless steel filtration under vacuum. The filtered, collagen dispersion is de-aired under vacuum. The uniform collagen dispersion is fed into a syringe pump which extrudes the collagen filaments through a modified 12 gauge needle at a rate of 1 ml per minute. The extruded wet collagen filaments are collected in a coacervation tank of acetate buffer pH 4.7 in the presence of 1% NaCl at 35° C. The coacervated collagen filaments are placed under a hood and dried by

air for 24 hours. The air dried filaments are crosslinked in a 0.1% glutaraldehyde solution in a phosphate buffered saline solution, pH 7.4, for 24 hours at room temperature. The crosslinked filaments are extensively washed in water and stored at room temperature until further use.

EXAMPLE 4

Fabrication of Ligament I Device

100 to 300 high density collagen filaments and 50 to 150 low density collagen filaments (ratio of 2:1) made in accordance with EXAMPLE 2 and 3 above are combined longitudinally into small bundles for braiding. Three bundle units of 40 cm long each are first braided at the mid-point. They are subsequently folded at the mid-point to form a small loop. Six bundle units are then braided to form a composite of collagen ligament containing two thirds high density collagen fibers intertwined with one third low density porous collagen fibers. The end of the ligament is sealed into a resorbable polymer mesh tube such as polylactate mesh tube. The thusly braided ligament can easily be stretched by 10 to 15% without strain the collagen molecules. Alternatively, the braided bundles may be folded to have a loop at each end.

EXAMPLE 5

Fabrication of Ligament II Device

Same as EXAMPLE 4 except that the high density collagen filaments are substituted by polylactate monofilaments obtained from Purac America, Inc., Chicago, Ill.

EXAMPLE 6

Fabrication of Ligament III Device

15 grams of purified collagen fibrils are swollen in 500 ml phosphate buffered saline (PBS) solution, containing 0.189 g of hyaluronic acid and 0.189 g of chondroitin sulfate to make a 3% (w/v) dispersion of collagen and 0.076% (w/v) of glycosaminoglycans. The rest of the procedure is the same as EXAMPLE 2. 15 grams of purified collagen fibrils are swollen in 500 ml phosphate buffered saline solution containing 0.189 g of hyaluronic acid and 0.189 g of chondroitin sulfate to make a 3% (w/v) dispersion of collagen fibrils and 0.076% (w/v) of glycosaminoglycans. The rest of the procedure is the same as EXAMPLE 3 except that collagen filaments are crosslinked in a 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide solution at pH 4.7 for 24 hours. The addition of carbodiimide is made every 3 to 4 hours, and the pH is adjusted to 4.7 after each addition of carbodiimide.

EXAMPLE 7

Description of Device Insertion

A 10 mm hole is drilled at the anatomic insertion site of the natural cruciate ligament on the femur and on the tibia. A guide suture is passed from the femur to the tibia. The guide suture is then attached to the loop at the end of the prosthetic ligament, and the ligament pulled across the joint. The ligament is fixed to the femur and the tibia by drilling a screw through the loop at the end of the ligament and into the cortical and cancellous bone. The knee is passed through a range of motion under direct visualization with either open or arthroscopic techniques. Any impinging bone is resected.

EXAMPLE 8

In Vitro and In Vivo Testing

In Vitro Testing

Each prosthetic ligament is mounted in an mechanical testing jig (MTS) with a post through each ligament end loop. The post is grasped in the mechanical jaws of the MTS force loading machine. The graft is pulled apart at a displacement rate of 15 mm/sec and compared to normal cruciate ligament strengths (estimated to be about 1500 to 2500 Newtons).

In Vivo Testing

Each Prosthetic ligament is implanted in an animal knee joint (e.g., dog, goat, monkey) and tested six months and twelve months after implantation. Following surgery the animals are allowed unrestricted cage and exercise activity for six or twelve months, at which time the animal is euthanized. Each knee is striped of extraarticular tissue. The femurs and tibias potted and loaded onto a MTS machine with the ACL aligned along the axis of the actuator. The joints are pulled apart at a displacement rate of 15 mm/sec as described by McCarthy et al. (Orthopedic Research Society Meeting, Washington, D.C. (1991).

The present invention may be embodied in other specific forms without departing from the spirit or essential characteristics thereof. The present embodiments are therefore to be considered in all respects as illustrative and not restrictive, the scope of the invention being indicated by the appended claims rather than by the foregoing description, and all changes which come within the meaning and range of equivalency of the claims are therefore intended to be embraced therein.

We claim:

1. A prosthetic ligament comprising a plurality of substantially aligned, elongated filaments,

each of said filaments being a dry, porous, volume matrix reconstituted from biocompatible and bioresorbable fibrils, said fibrils being short segments of fibers of a polymeric connective tissue-type component, or analog thereof, at least some of said fibrils being crosslinked,

at least one of said filaments being a high density filament having a density of about 1.0 to about 1.3 g/cm^3

wherein each of said filaments establishes a bioresorbable scaffold adapted for ingrowth of ligament fibroblasts, and wherein said scaffold and said ingrown fibroblasts support natural ligament tensile forces.

2. The prosthetic ligament of claim 1, wherein said filaments comprise low density filaments having a density of about 0.05 to about 0.40 g/cm^3.

3. The prosthetic ligament of claim 2, wherein the density of said low density filaments is from about 0.07 to about 0.30 g/cm^3.

4. The prosthetic ligament of claim 1, wherein each of said fibrils are segments of a polymeric connective tissue-type component selected from the group consisting of collagen, elastin, reticulin, cellulose, alginic acid, chitosan, and analogs thereof, and mixtures thereof.

5. The prosthetic ligament of claim 4, wherein said fibrils comprise segments of collagen.

6. The prosthetic ligament of claim 1, wherein said crosslinks are formed by a chemical crosslinking reagent.

7. The prosthetic ligament of claim 6 wherein said crosslinking reagent is selected from the group consisting of glutaraldehyde, formaldehyde, carbodiimides, hexamethylene diisocyanate, bisimidates, polyglycerol polyglycidyl ether, glyoxal, adipyl chloride and mixtures thereof.

8. The prosthetic ligament of claim 7, wherein said crosslinking agent is formaldehyde.

9. The prosthetic ligament of claim 1, wherein said filaments further comprise a plurality of polysaccharide molecules interspersed with said fibrils.

10. The prosthetic ligament of claim 9, wherein at least a portion of said polysaccharide molecules provide crosslinks between ones of said fibrils.

11. The prosthetic ligament of claim 9, wherein said fibrils are present at a concentration of about 75 to 100% by dry weight, and said polysaccharide molecules are present at a concentration of about 0 to 25% by dry weight.

12. The prosthetic ligament of claim 9, wherein said polysaccharide molecules are selected from the group consisting of chondroitin 4-sulfate, chondroitin 6-sulfate, keratan sulfate, dermatan sulfate, heparan sulfate, heparin, alginic acid, chitosan, hyaluronic acid, and mixtures thereof.

13. The prosthetic ligament of claim 9, wherein polysaccharide molecules are dispersed substantially uniformly throughout said matrix.

14. The prosthetic ligament of claim 9, wherein said polysaccharide molecules are dispersed substantially non-uniformly throughout said matrix.

15. The prosthetic ligament of claim 1, wherein said fibrils are oriented in a substantially random fashion throughout said filament.

16. The prosthetic ligament of claim 1, wherein said fibrils are oriented in a substantially ordered fashion throughout said filament.

17. The prosthetic ligament of claim 1, further comprising a mesh extending from a portion of the outer surface of said filament, said mesh being resorbable and biocompatible.

18. A method of regenerating ligamentous tissue in vivo comprising the steps of:

a) providing a prosthetic ligament comprising a plurality of substantially aligned, elongated filaments in a mutually adjacent relationship,

each of said filaments being a dry, porous, volume matrix reconstituted from biocompatible and bioresorbable fibrils, said fibrils being short segments of fibers of a polymeric connective tissue-type component, or analogs thereof, at least some of said fibrils being crosslinked,

at least one of said filaments being a high density filament having a density of about 1.0 to about 1.3 g/cm^3

wherein each of said filaments establishes a bioresorbable scaffold adapted for ingrowth of ligament fibroblasts; and

b) implanting said prosthetic ligament into a joint by surgical procedures,

said implanted prosthetic ligament and said ingrown fibroblasts supporting normal ligament tensile forces.

19. The method of claim 18, wherein said providing step (a) comprises providing a prosthetic ligament including a plurality of polysaccharide molecules interspersed with said fibrils.

20. The method of claim 18, wherein said providing step (a) includes fabricating said prosthetic ligament, said fabricating step comprising the steps of:

(a) providing a plurality of essentially pure fibers of a polymeric connective tissue-type component selected from the group consisting of collagen, elastin, reticulin, cellulose, alginic acid, chitosan, and analogs thereof, and mixtures thereof;

(b) cutting said fibers into segments shorter than said fibers to form fibrils;

(c) aggregating said fibrils into a plurality of elongated filaments;

(d) contacting said filaments with a crosslinking reagent for a time sufficient to crosslink at least a portion of said fibrils within said filaments, whereby each filament forms a dry, porous, volume matrix adapted for the ingrowth of ligament fibroblasts; and

(e) aligning a plurality of said filaments in mutually adjacent relationship, said aligned filaments forming said prosthetic ligament.

21. The method of claim 18, wherein said providing step (a) includes fabricating said prosthetic ligament, said fabricating step further comprising aggregating said fibrils with a plurality of polysaccharide molecules to form a plurality of elongated filaments.

* * * * *

US006106556A

United States Patent [19]

Demopulos et al.

[11] Patent Number: 6,106,556

[45] Date of Patent: Aug. 22, 2000

[54] TENDON AND LIGAMENT REPAIR SYSTEM

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[73] Assignee: **Omeros Medical Systems, Inc.**, Seattle, Wash.

[*] Notice: This patent is subject to a terminal disclaimer.

[21] Appl. No.: **09/182,759**

[22] Filed: **Oct. 29, 1998**

Related U.S. Application Data

[63] Continuation-in-part of application No. 09/086,126, May 28, 1998, which is a continuation of application No. 08/567,311, Dec. 4, 1995, Pat. No. 5,800,544, which is a continuation-in-part of application No. 08/349,358, Dec. 2, 1994, abandoned.

[51] **Int. Cl.**[7] **A61F 2/08**

[52] **U.S. Cl.** **623/13.16**; 623/13.18; 606/72; 606/59

[58] **Field of Search** 623/11, 13, 13.15, 623/13.16, 13.18, 13.13, 13.14, 13.12, 13.11, 11.11; 606/53, 72, 59, 71

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Primary Examiner—Paul B. Prebilic
Attorney, Agent, or Firm—Christensen O'Connor Johnson & Kindness PLLC

[57] **ABSTRACT**

A rigid or semi-rigid reinforcement member is inserted into or over the damaged portion of an injured tendon or ligament. The tendon or ligament is connected to the reinforcement member such that the cord-member combination can immediately withstand normal tensile forces. The interconnection can be mechanical, such as by pins extending through the sleeve reinforcement member and cord. The sleeve can be bioabsorbable over a sufficiently long period of time that the cord is healed by the time the sleeve is absorbed.

23 Claims, 12 Drawing Sheets

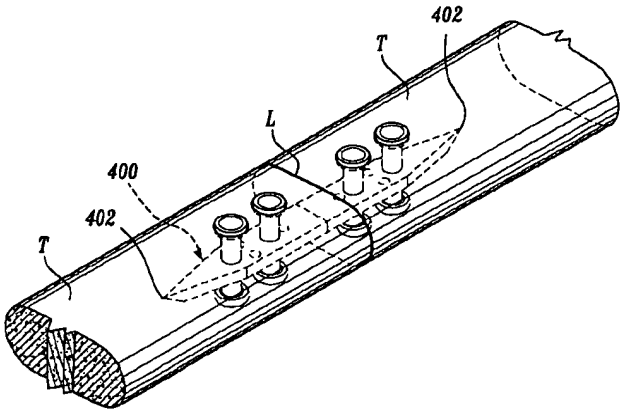

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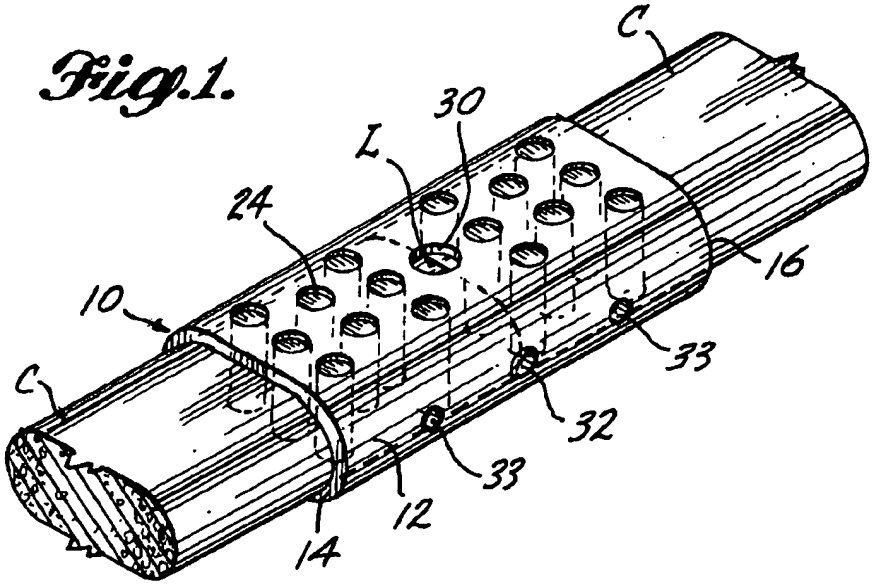
Fig.1.



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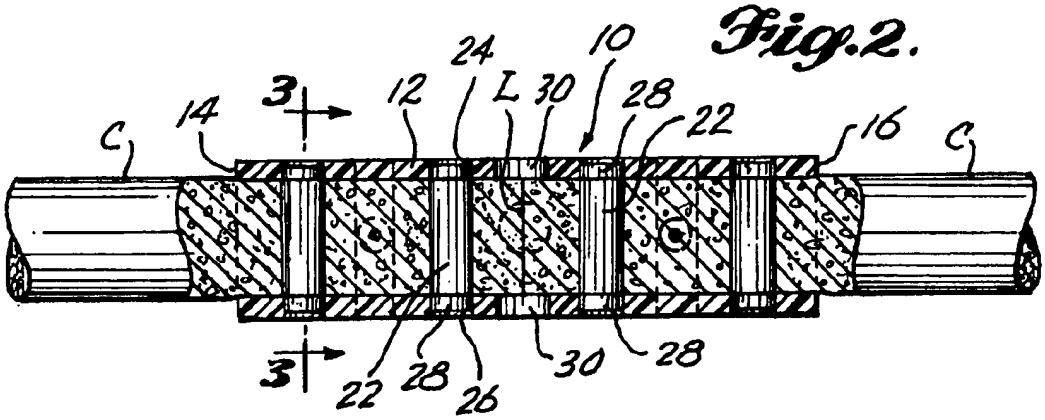

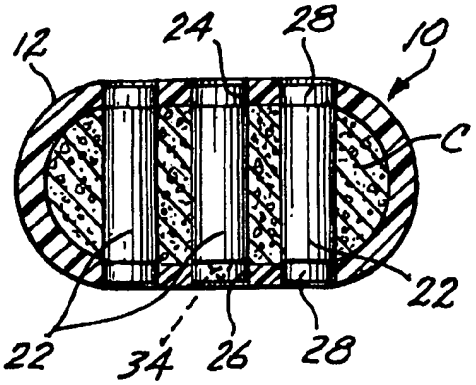

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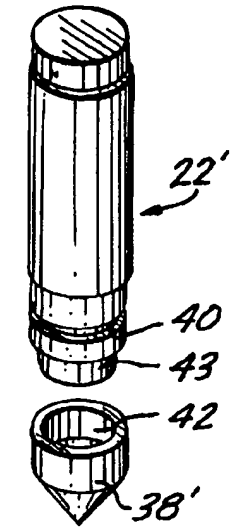

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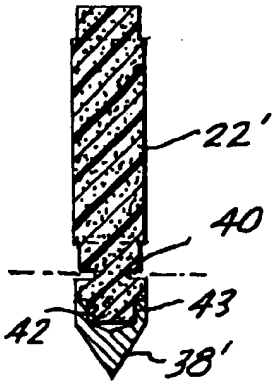

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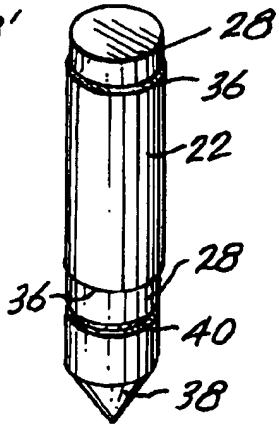

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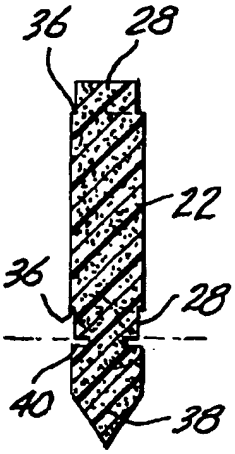

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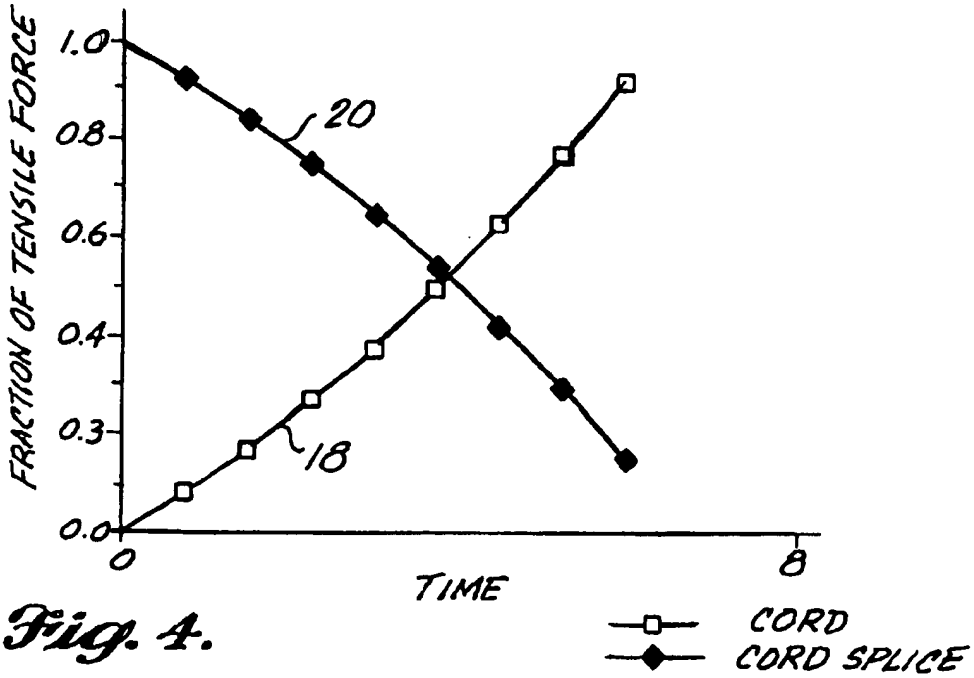

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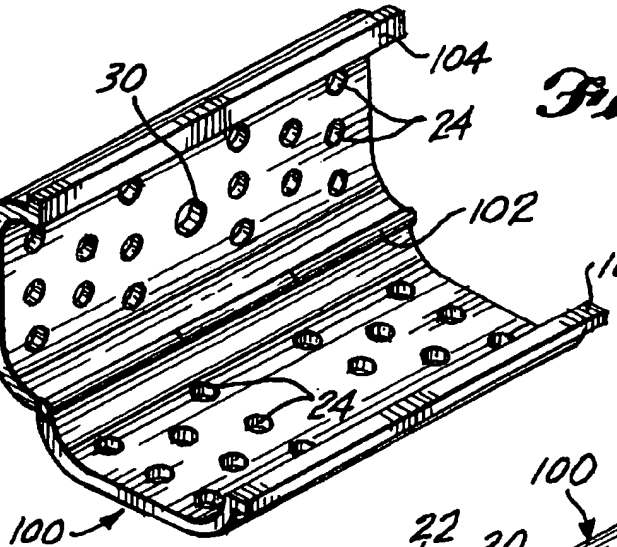

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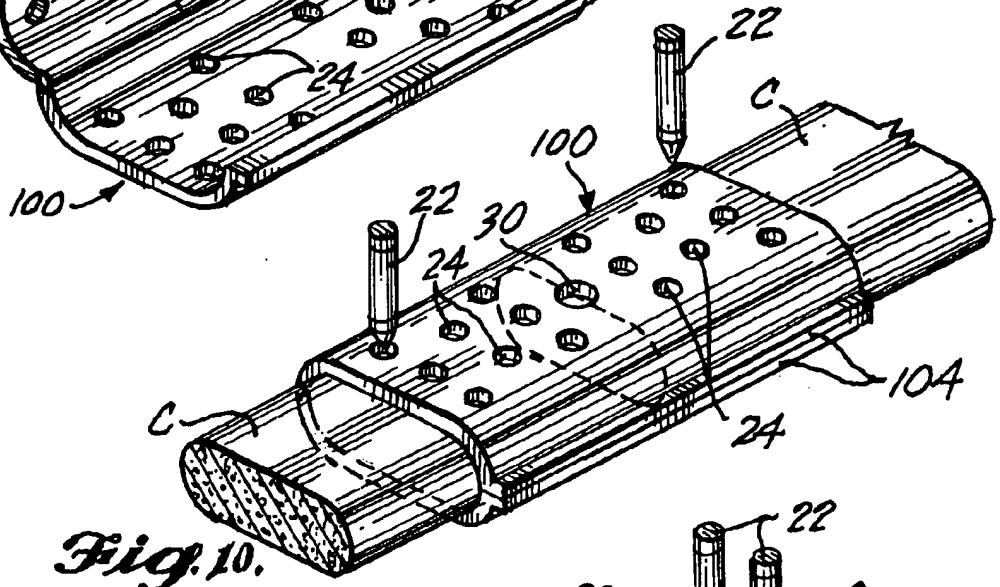

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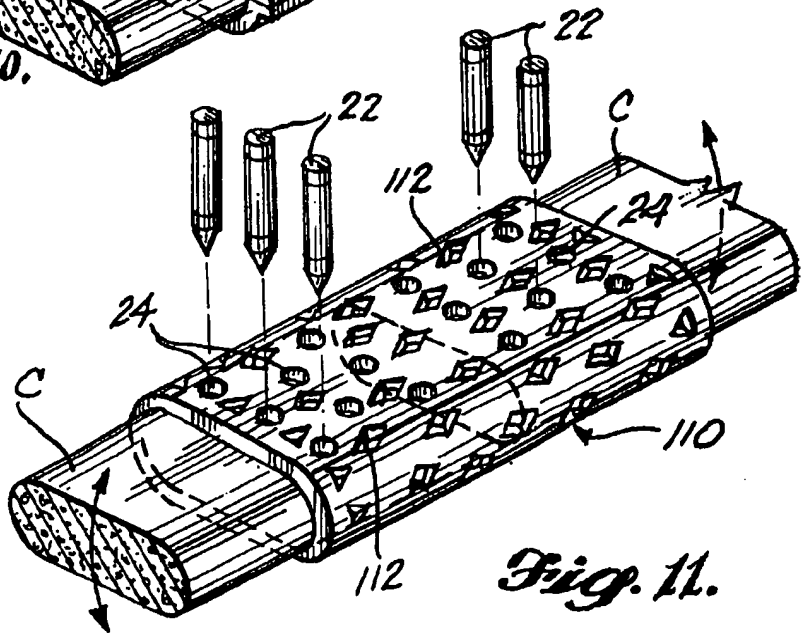

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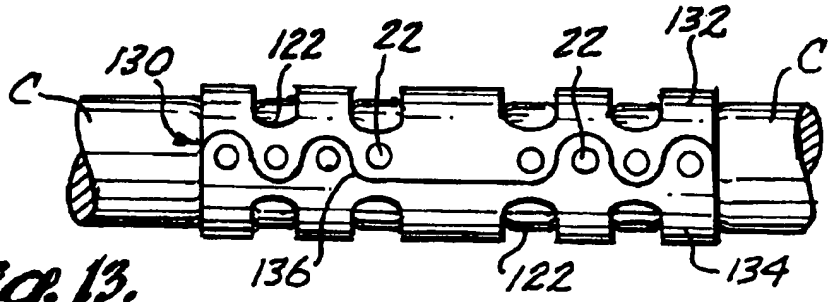
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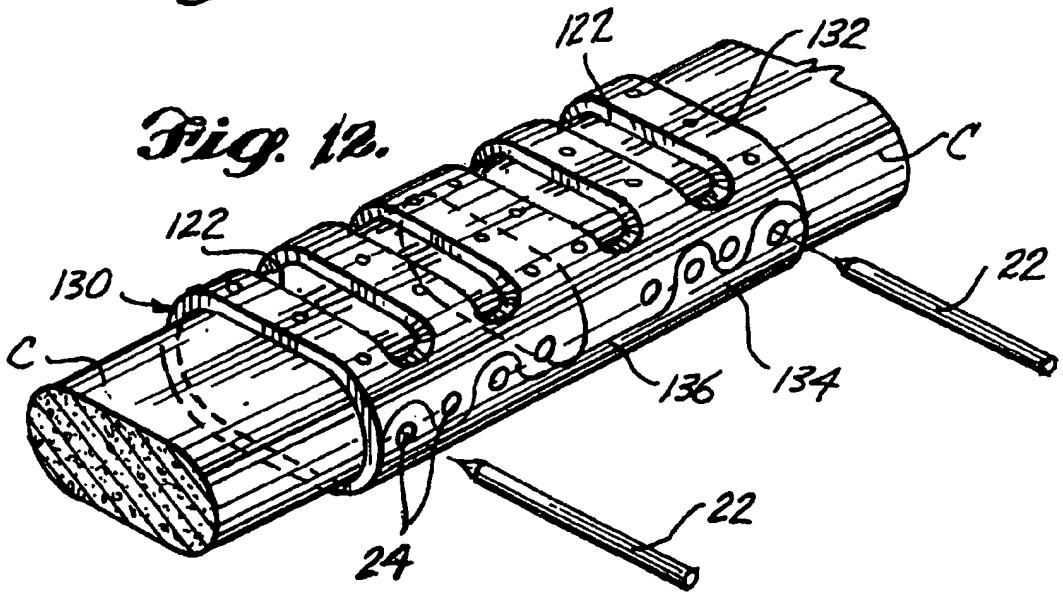
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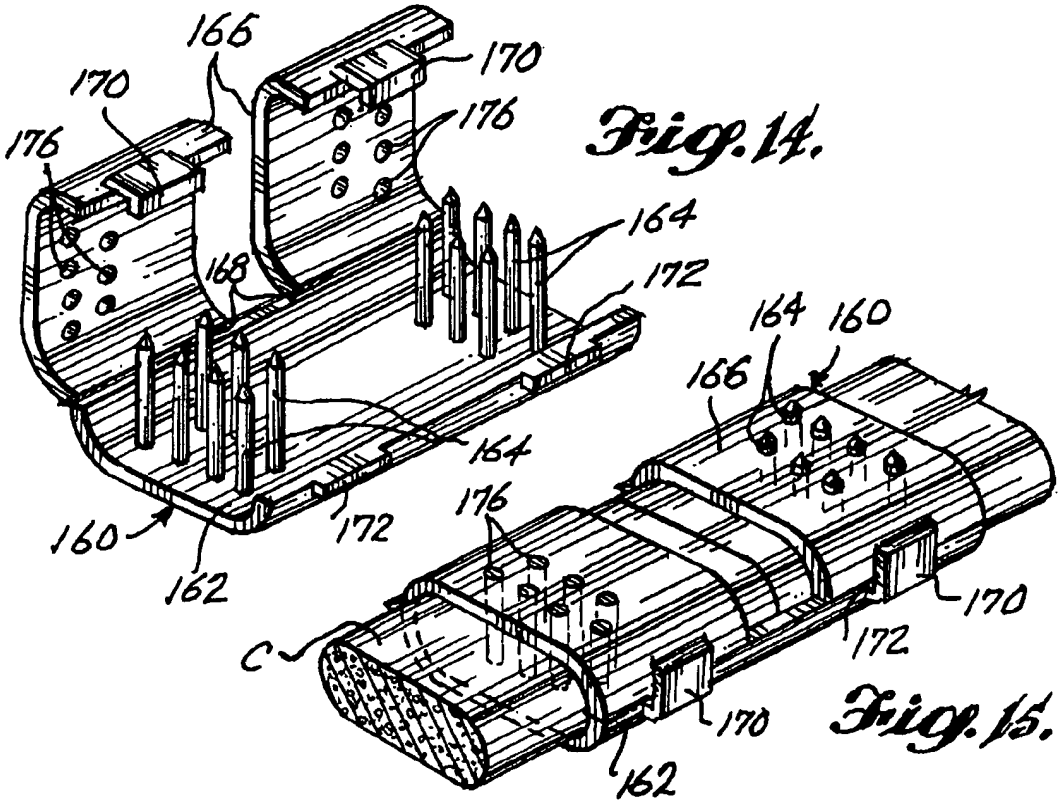
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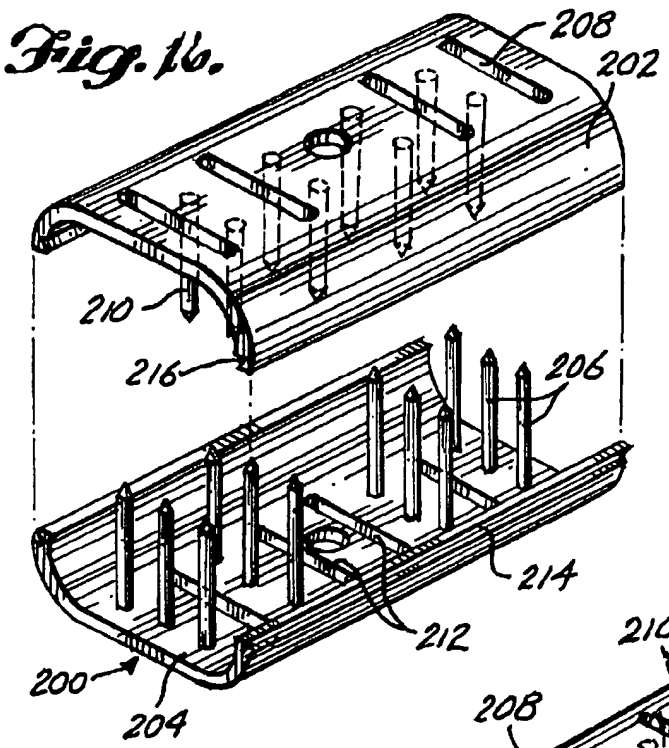
Fig. 14.

Fig. 15.



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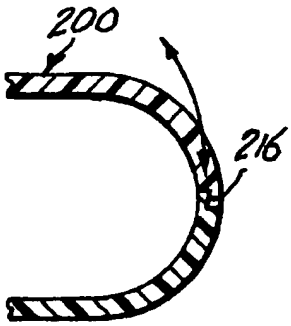

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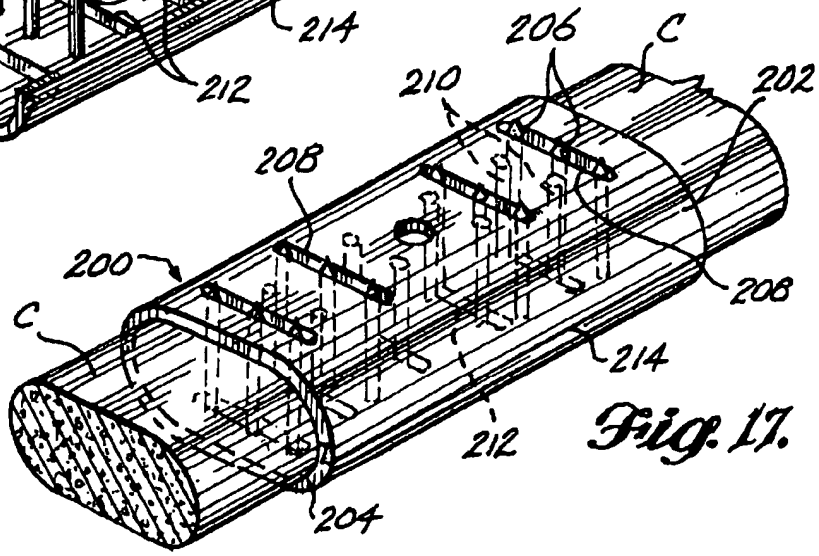

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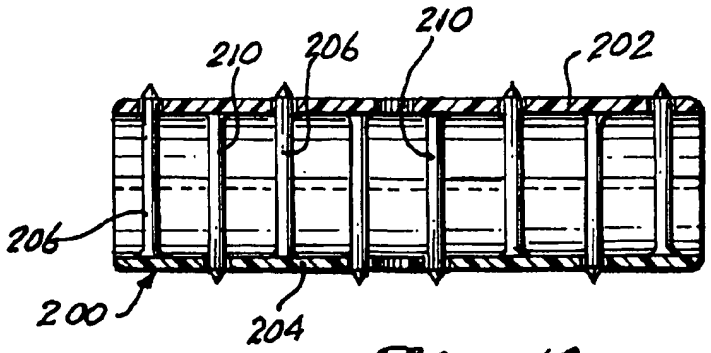

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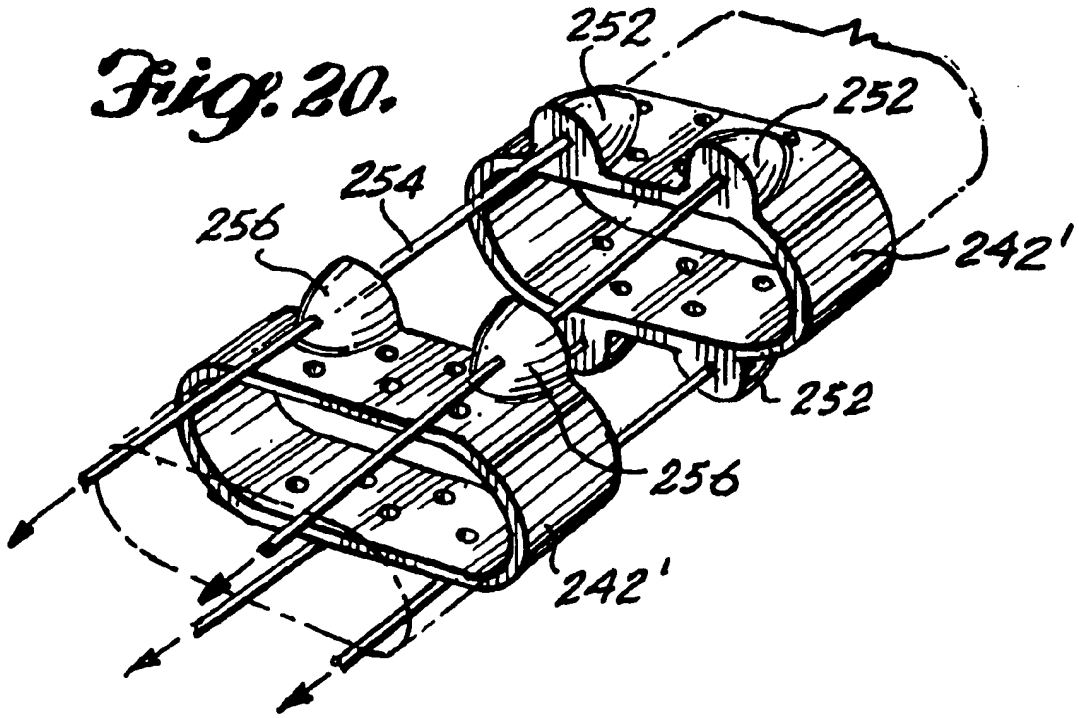

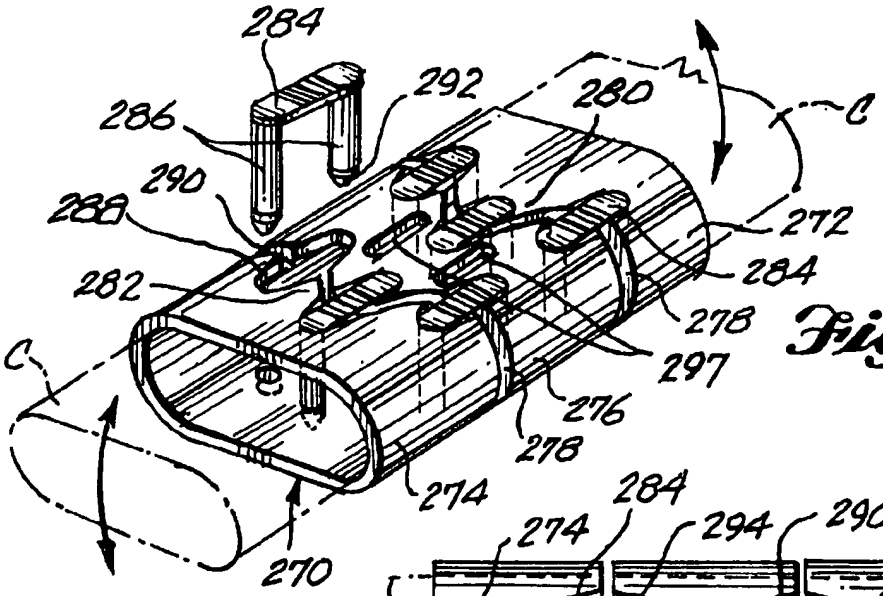

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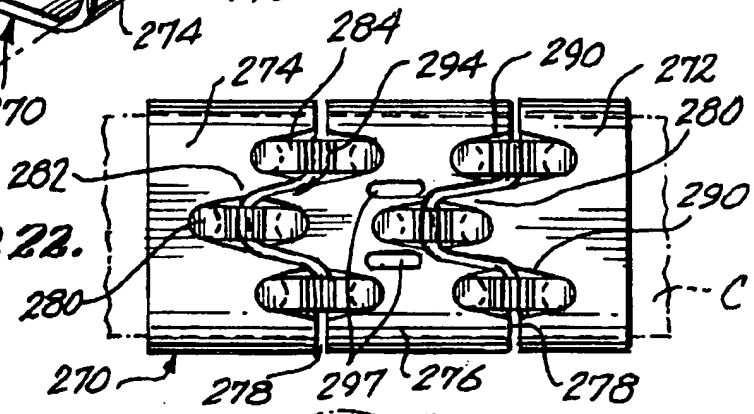

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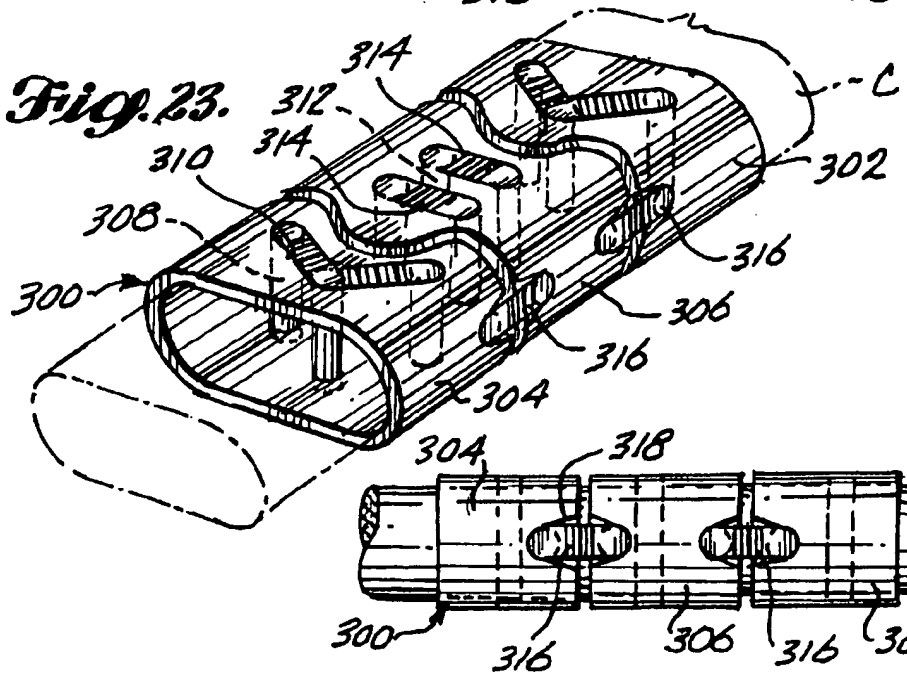

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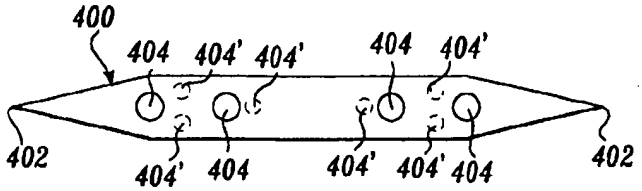

Fig. 25.

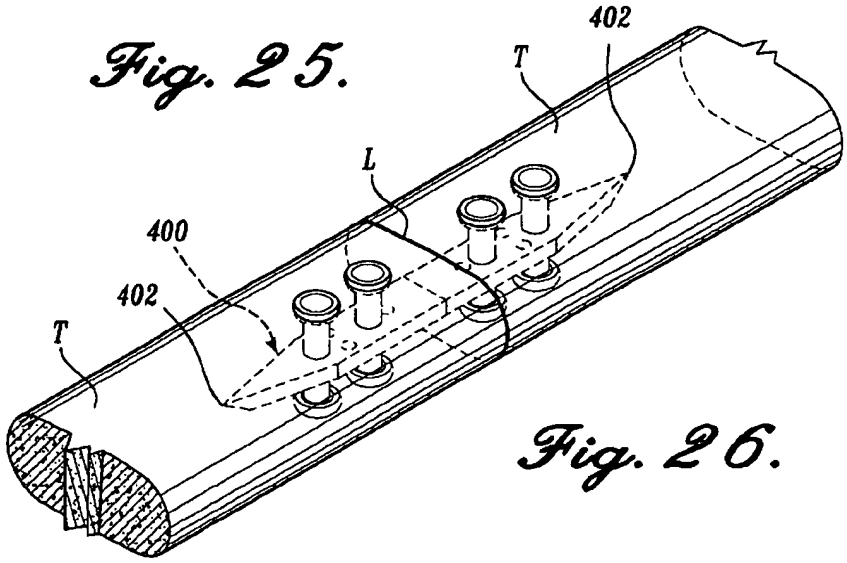

Fig. 26.

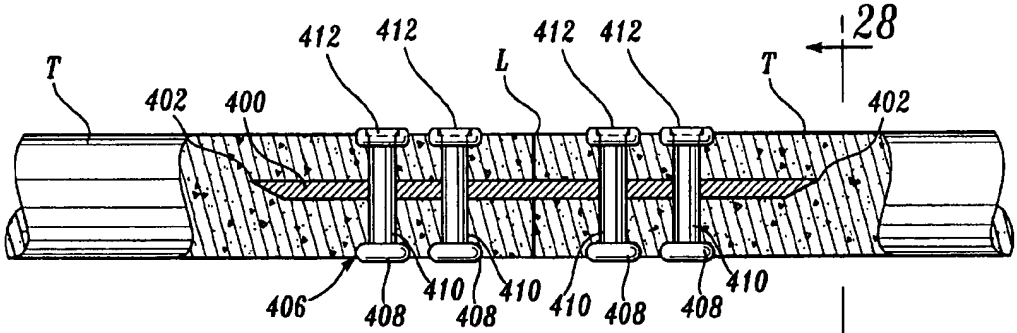

Fig. 27.

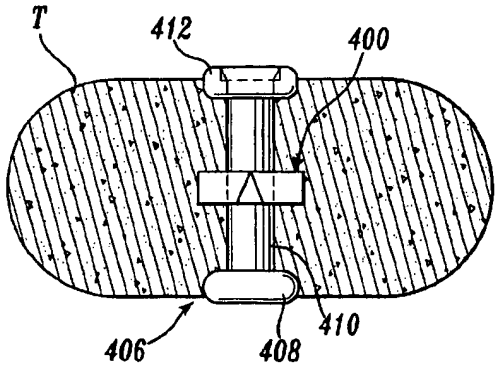

Fig. 28.

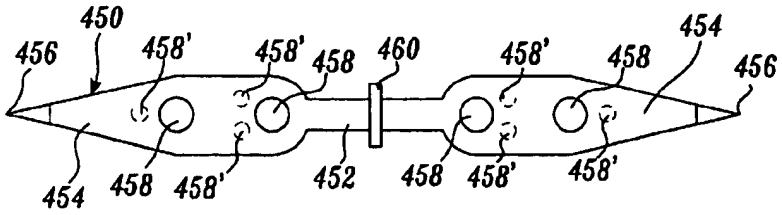

Fig. 29.

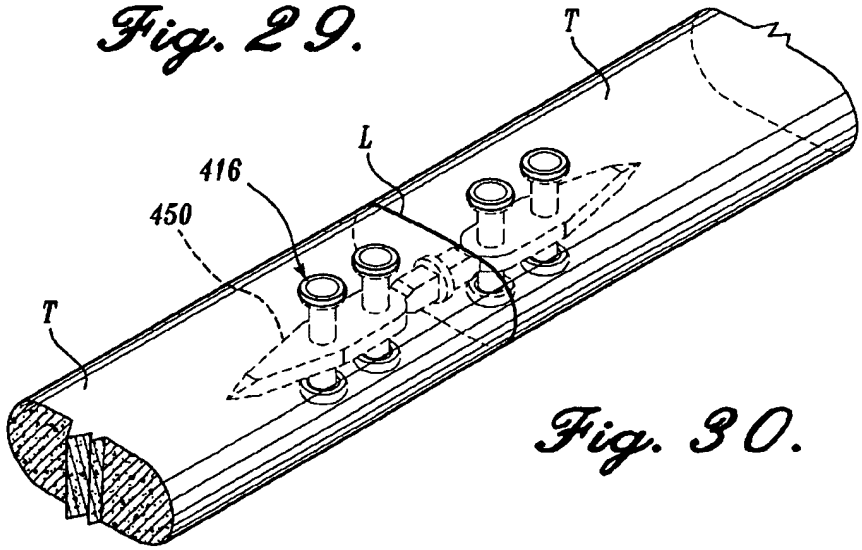

Fig. 30.

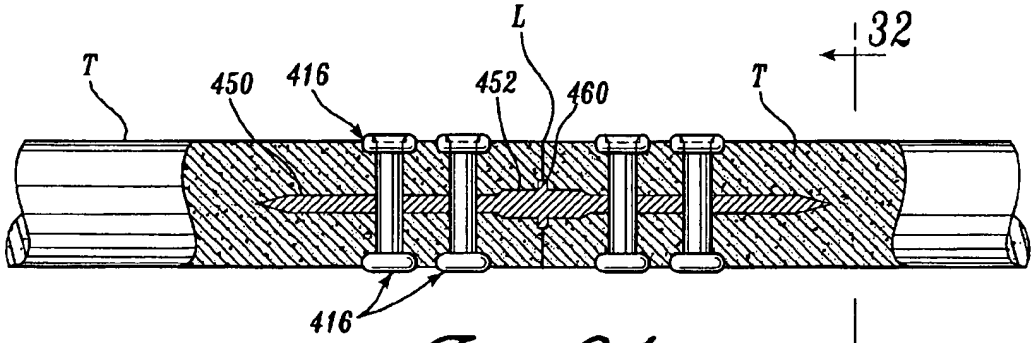

Fig. 31.

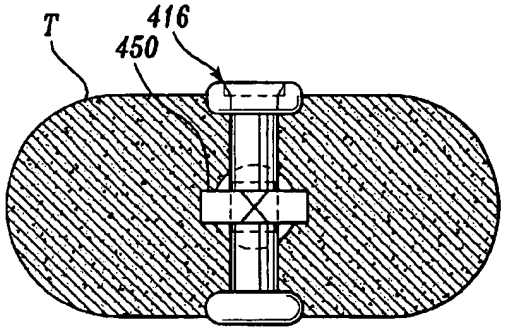

Fig. 32.

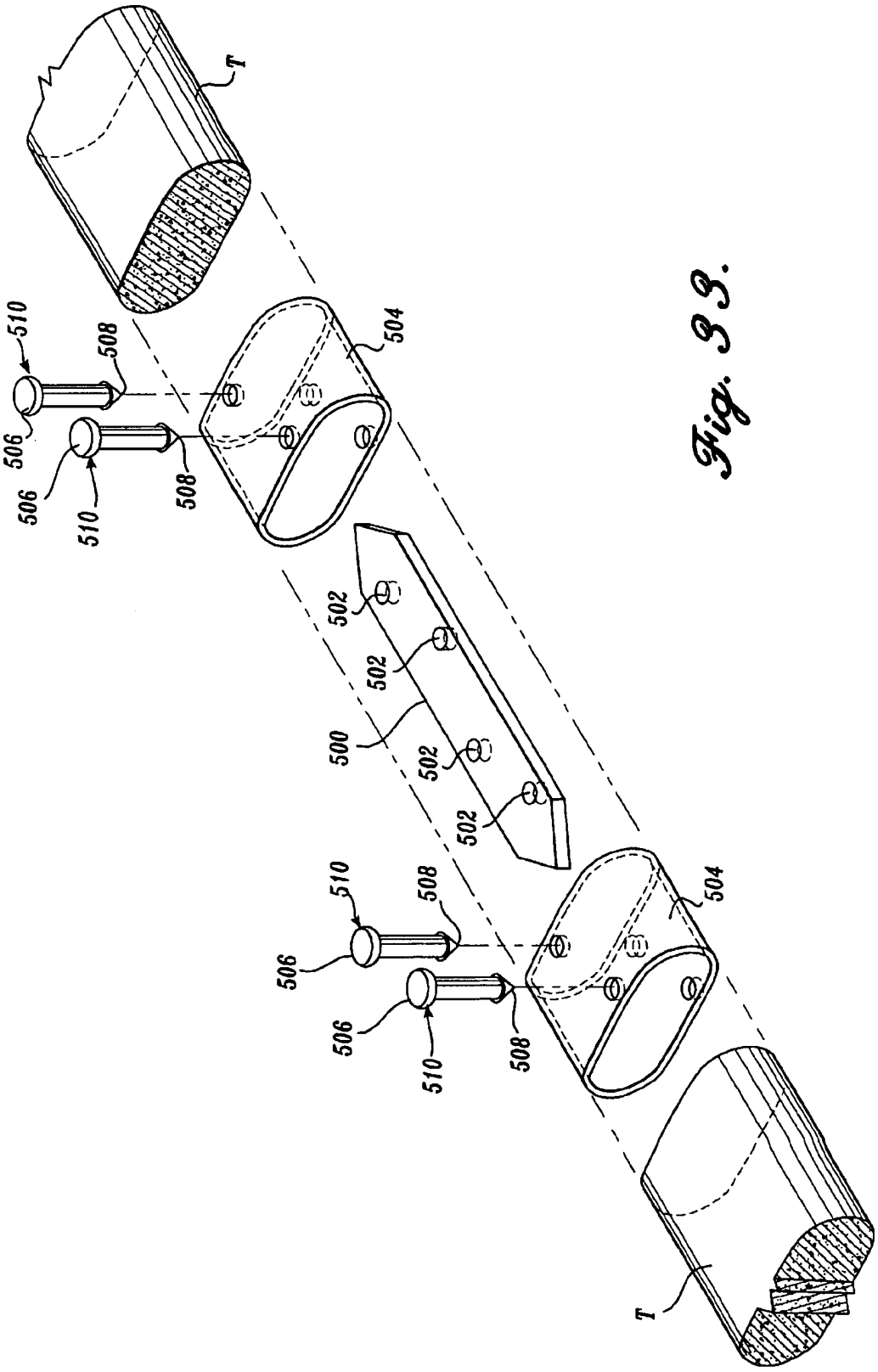
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Fig. 33.

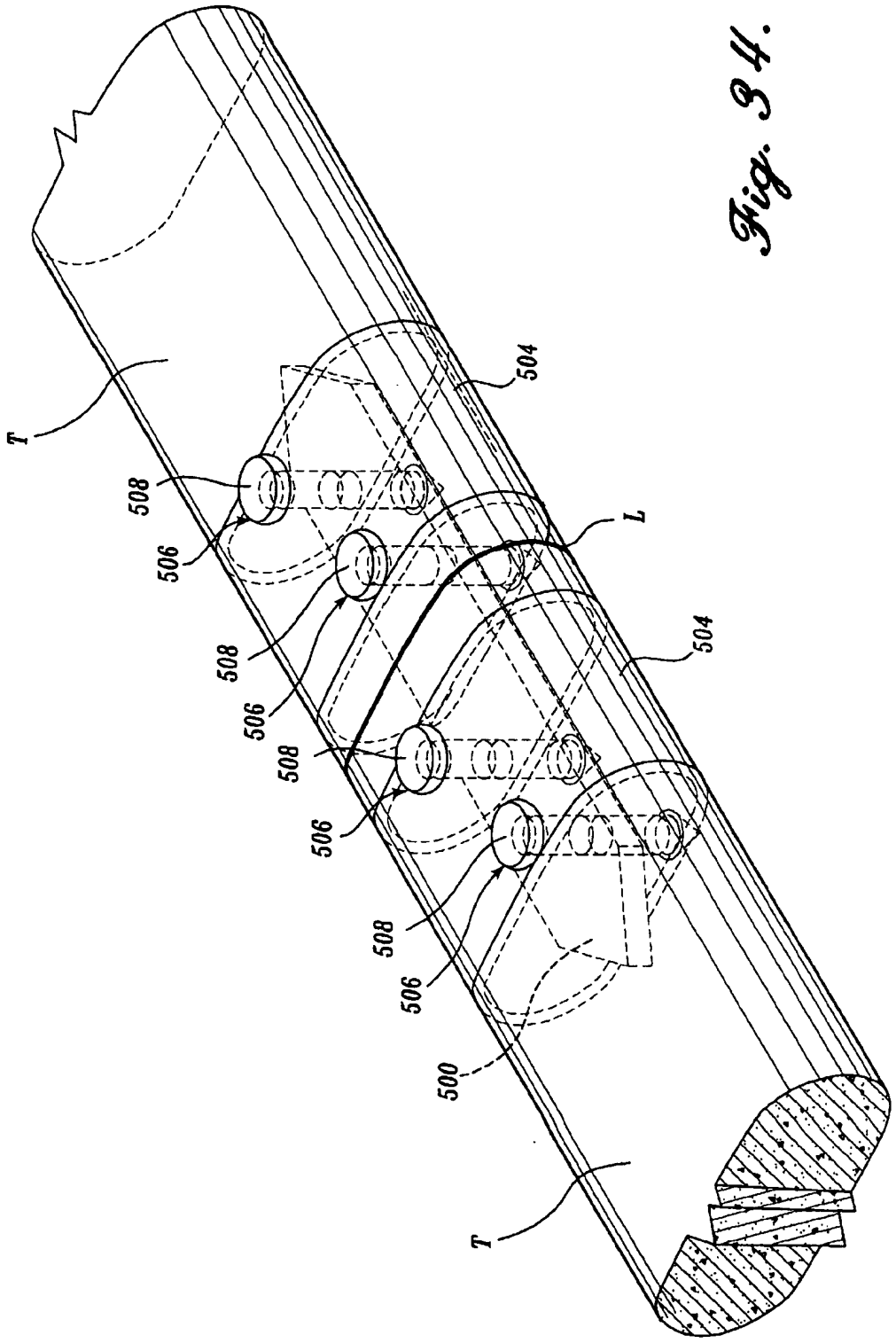

Fig. 34.

TENDON AND LIGAMENT REPAIR SYSTEM

This application is a continuation-in-part of U.S. patent application Ser. No. 09/086,126, filed on May 28, 1998, titled "TENDON AND LIGAMENT REPAIR SYSTEM," which is a continuation of U.S. patent application Ser. No.08/567,311, filed on Dec. 4, 1995, titled "TENDON AND LIGAMENT REPAIR SYSTEM," now U.S. Pat. No. 5,800,544, which is a continuation-in-part of U.S. patent application Ser. No. 08/349,358, filed on Dec. 2, 1994, titled "TENDON AND LIGAMENT SPLICE," now abandoned, all of which are expressly incorporated by reference herein; and this application claims the benefit of U.S. Provisional Application No. 60/063,892, filed on Oct. 29, 1997.

FIELD OF THE INVENTION

The present invention relates to a system for repairing lacerated or severed fibrous connective tissue, referred to herein as "connective cords" or "cords," particularly tendons and ligaments.

BACKGROUND OF THE INVENTION

Repair techniques for lacerated or severed tendons and ligaments ("connective cords" or "cords") vary widely depending on the nature of the injury and the particular cord affected. There are large differences in the extent to which access can be obtained in the least obtrusive manner, in the amount of cord excursion, in the surrounding environment, in the stresses to which different cords are normally subjected, and in the healing characteristics of different cords. In addition, often there is no consensus of the overall best way to repair a given cord. Examples of often injured cords having different accepted repair techniques are flexor tendons of the hand and the anterior cruciate ligament (ACL) of the knee.

For example, repair of a long flexor tendon that has been severed is typically achieved by suturing the severed tendon ends face-to-face. Historically, the joints across which the tendon acts were immobilized for from three to eight weeks to protect the tendon while it healed, because a freshly sutured tendon can withstand only a fraction of the tensile force to which a healthy tendon is subjected during normal use. Immobilization results in scarring and adhesion formation along the length of the tendon. Range of motion is adversely affected, particularly in the case of flexor tendons which normally glide smoothly through and over the unique system of tendon tunnels and pulleys of the hand. Nevertheless, it was thought that fibroblastic ingrowth was required in order for the tendon to heal, such that immobilization and the resulting decreased range of motion were considered necessary evils in order for effective healing to take place. More recently it has been discovered that flexor tendons have an intrinsic capacity to heal and that limited motion will actually expedite healing. Still, exercises must be carefully planned and carried out due to the weakness of the sutured repair. In early stages of healing, protected passive and/or restricted active exercises may be used, followed by tendon gliding and active strengthening exercises in later stages. The affected joints are most often partially immobilized to prevent inadvertent application of excess force.

In the case of an anterior cruciate ligament (connecting the bottom of the femur and the top of the tibia) the stresses resulting from applied forces are much greater, there is less interaction with surrounding tissue and bone, the excursion of the cord is less, and the healing tendencies are vastly different. Despite numerous studies, there still is no universally accepted repair procedure, and prevailing procedures are difficult and intricate. The current "standard of care" remains the reconstruction of the ACL using a bone-tendon-bone or tendon autograft (i.e., harvested from the patient). However, there are multiple problems with autografting: (1) the intact ACL possesses important mechanoreceptive and proprioceptive capabilities, and graft reconstruction sacrifices these capabilities; (2) autografting involves considerable donor site morbidity; (3) to avoid donor site morbidity, occasionally a cadaveric graft is used, which carries the risk of disease transmission.

These problems with ACL reconstruction have led to renewed interest in primary repair of the ACL. In the case of primary repair without augmentation, small bores are drilled in the adjacent bones approximately at the anatomically correct sites for normal connection of the ACL. Multiple loops of suture are used for reconnecting the ligamentous stumps to the bone. Several loops of permanent suture can provide an initial strong repair. However, over time the strength of the repaired ACL often decreases, which is indicative of a failure in the healing process. In general, it is now accepted that healing tendencies of the intra-articular ACL are poor, particularly when compared to the neighboring extra-articular medial collateral ligament which heals readily.

Failure or long-term weakening of ACL primary repair has led to techniques for "augmenting" a primary repair. These can involve suturing biological material, such as a section of patellar tendon, across a repair site, and the use of artificial augmenting strips or sheaths which typically have been flexible and fibrous in the hope that healing of the ACL will be promoted, rather than being inhibited by, the close proximity of an artificial "shield." Strips or bands of Dacron, polyethylene or carbon fiber have had their opposite ends stapled or otherwise anchored to the adjacent bones to provide the primary or secondary support for the "healing" ACL.

SUMMARY OF THE INVENTION

The present invention provides a system for repair of injured connective cords by application of a reinforcing member of substantially rigid or semi-rigid material, such member being adapted for extending longitudinally between severed end portions of a connective cord with the severed end portions in abutting relationship, and securing the cord to the reinforcing member such that tension applied to the cord is transmitted through the reinforcing member. The reinforcing member and mechanism securing it to the cord maintain the severed cord ends abutting as tension is applied to the cord by transmitting tensional force through the reinforcing member. In one aspect of the present invention, the severed ends of the cord are secured to the reinforcing member by a plurality of pins anchored in the reinforcing member and extending at least part way through the connective cord for transmission of tensional force from the connective cord through the pins and the reinforcing member. The reinforcing member can extend internally or externally of the cord. For example, the affected cord ends can be enclosed in a hollow reinforcing sleeve and the adjacent end portions of the cord secured inside the sleeve. In other embodiments, the reinforcing member can be inserted internally of the adjacent cord end portions, and such end portions secured to the internal reinforcing member. Connection pins can be arranged in rows with pins of adjacent rows staggered and with adjacent pins spaced apart sufficiently to prevent inordinate localized stresses from being applied to the tissue when the tendon is tensioned.

In the case of a tendon that normally glides along adjacent tissue and/or bone, it is important that the reinforcing member and mechanical connection components not interfere with the gliding motion. The mechanical interconnection of the cord ends and the reinforcing member preferably is sufficiently strong that immobilization is not required. Strengthening and healing promoting exercises can begin almost immediately.

The reinforcing member and any mechanical connection components can be bioabsorbable. The period of bioabsorbability is selected based on the healing characteristics of the affected connective cord. Ideally, the reinforcing member and mechanical connection components will remain sufficiently strong over time such that the overall force that the repaired connective cord can withstand always is at least as great as the force to which it is normally subjected. For example, in the early stages when the cord itself has essentially no resistance to separation, the reinforcing member and connection components will withstand a strong tensile force. As the connective cord heals and is capable of withstanding substantial force on its own, the partially absorbed reinforcing member and connection components need not withstand as much force as at the outset.

BRIEF DESCRIPTION OF THE DRAWINGS

The foregoing aspects and many of the attendant advantages of this invention will become more readily appreciated as the same becomes better understood by reference to the following detailed description, when taken in conjunction with the accompanying drawings, wherein:

FIG. **1** is a top perspective of a severed fibrous cord of connective tissue repaired in accordance with one aspect of the system of the present invention;

FIG. **2** is a side elevation of the repaired cord of FIG. **1**, with parts broken away;

FIG. **3** is a vertical transverse section along line **3—3** of FIG. **2**;

FIG. **4** is a graph illustrating the relative strengths of a splice in accordance with the present invention and a healing connective cord over time;

FIG. **5** is a top perspective of a component of the splice in accordance with the present invention, namely, a connection pin, and

FIG. **6** is a longitudinal section thereof;

FIG. **7** is a top perspective of an alternative connection pin, with parts shown in exploded relationship, and

FIG. **8** is a longitudinal section thereof with parts assembled;

FIG. **9** is a top perspective of an alternative splice in accordance with the present invention, and

FIG. **10** is a corresponding top perspective of the splice of FIG. **9** with parts in different positions;

FIG. **11** is a top perspective of another embodiment of a splice in accordance with the present invention;

FIG. **12** is a top perspective of another alternative form of a splice in accordance with the present invention, and

FIG. **13** is a side elevation of the splice of FIG. **12**;

FIG. **14** is a top perspective of an alternative splice in accordance with the present invention, and

FIG. **15** is a top perspective of the splice of FIG. **14** with parts in different positions;

FIG. **16** is a top perspective of another embodiment of a splice in accordance with the present invention, with parts shown in exploded relationship,

FIG. **17** is a top perspective corresponding to FIG. **16** but with parts assembled,

FIG. **18** is a longitudinal vertical section of the assembled splice of FIG. **17**, and

FIG. **19** is a fragmentary transverse vertical section of the assembled splice of FIG. **17**;

FIG. **20** is a top perspective of another form of a splice in accordance with the present invention with parts partially assembled;

FIG. **21** is a top perspective of another embodiment of a splice in accordance with the present invention, with some parts shown in exploded relationship, and

FIG. **22** is a fragmentary enlarged top plan of a portion of the splice of FIG. **21**;

FIG. **23** is a top perspective of another embodiment of a splice in accordance with the present invention, and

FIG. **24** is a fragmentary side elevation of a portion thereof;

FIG. **25** is a top plan of an internal reinforcement member usable in a repair system in accordance with the present invention,

FIG. **26** is a top perspective of a severed fibrous cord repaired in accordance with the present invention using the reinforcement member of FIG. **25**,

FIG. **27** is a side elevation of the repaired cord of FIG. **26**, with parts broken away, and

FIG. **28** is a vertical transverse section along line **28—28** of FIG. **27**;

FIG. **29** is a top plan of an alternative reinforcement member usable in a repair system in accordance with the present invention,

FIG. **30** is a top perspective of a severed cord repaired using the reinforcement member of FIG. **29**,

FIG. **31** is a side elevation of the repaired cord of FIG. **30**, with parts broken away, and

FIG. **32** is a transverse vertical section along line **32—32** of FIG. **31**; and

FIG. **33** is a top perspective of a severed cord repaired with another embodiment of a repair system in accordance with the present invention, with parts shown in exploded relationship, and

FIG. **34** is a top perspective corresponding to FIG. **33**, but with parts assembled.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

The present invention is used for repairing lacerated or severed fibrous connective tissue ("connective cords"), particularly ligaments and tendons. One embodiment of a splice **10** in accordance with the invention is illustrated in FIGS. **1**, **2** and **3** in conjunction with a connective cord C, such as a flexor tendon, separated at a location L intermediate its opposite end connections (not shown) to adjacent bone and muscle. Relative sizes of the cord and splice components are exaggerated in the drawings for ease of illustration and description.

The primary component of the splice **10** is a unitary, substantially rigid or semi-rigid reinforcement member, in this case a sleeve **12**. The interior of the sleeve is of substantially uniform cross section from one end **14** to the other end **16**, sized to snugly receive the severed end portions of the cord. The separation location L is situated midway between the sleeve ends. In accordance with the

present invention, the cord end portions are secured within the sleeve so as to maintain the separated ends in abutting relationship to promote healing. In addition, the severed end portions are interconnected with the sleeve for substantially uniform distribution of force across the cord. Tension can be applied to the cord through the splice even before any healing has occurred, thereby enabling normal functioning of the repaired cord immediately or soon after the repair. Thus, in characterizing the sleeve as preferably being "rigid or semi-rigid", one important characteristic is that the dimensions and general shape of the sleeve not change substantially as normal tension is applied to a cord secured in the sleeve, it being particularly important that force applied to the cord be transmitted through the sleeve. In the case of a severed cord, it is desirable for the severed ends of the cord to abut within the sleeve and maintain the abutting relationship despite tension being applied to the cord. Further, as described in more detail below, in the case of mechanical fasteners for securing a cord within the sleeve, preferably the rigid or semi-rigid character of the sleeve results in the fasteners being stably positioned without substantial deflection caused by tension applied to the cord.

For many connective cords, including flexor tendons, severed cord ends maintained in abutting relationship will heal over time and gradually regain the pre-injury strength. In accordance with the present invention, the splice **10** can be formed of a rigid or semi-rigid bioabsorbable polymer. The ideal relationship of the strength of the splice as compared to the strength of the healing cord is illustrated in FIG. **4**. As represented by line **18**, initially (time "0") the abutting severed cord ends will not inherently withstand tension whereas, as represented by line **20**, at t=0 the splice and cord connection will withstand the entire maximum force to which the cord would be subjected in normal use. The splice weakens as it is absorbed into the body, as indicated by the downward slope of line **20**. At the same time, the repair site heals and strengthens. Ideally, at each stage of healing the combined strength of the splice and the healing cord is at least equal to the maximum force to which the cord is normally subjected. In the case of a flexor tendon, normal healing is completed by about twelve weeks, at which time the tendon itself usually will withstand normal forces and the splice is no longer required. An appropriate blend of bioabsorbing polymer, such as polydioxanone (PDO), polyglycolic acid (PGA), polylactic acid (PLA) or a PGA/PLA copolymer, can be selected based on the healing characteristics of the particular connective cord repaired and the dimensional requirements for the splice in order to achieve the desired strength and bioabsorbing properties. In addition, the sleeve and/or the components securing it to the cord can be coated or impregnated with an agent or agents to enhance healing or decrease adhesion or scar formation such as hyaluronic acid, angiogenic factors, growth factors and/or collagenase inhibitors. Such agents can immediately diffuse into the body directly adjacent to the repair, and/or be released over time as the sleeve is absorbed.

In the case of connective cords that move along or through adjacent tissue, bone, etc., and particularly in the case of flexor tendons which pass through a series of fibro-osseous tunnels and pulleys of the hand, the cross-sectional shape of the sleeve **12** should approximate the shape of the connective cord when moving under tension. In the case of a flexor tendon, the cord is oval when under tension and, accordingly, the shell **12** is of oval cross section. In a representative application repairing a flexor tendon, the shell can have an inside upright minor axis dimension of about 0.094 inch and an inside horizontal major axis dimension at least about twice the length of the minor axis. The length of the splice shell must be large enough to allow securing of a sufficient segment of each severed end portion without application of localized forces that could further tear, lacerate or otherwise injure the cord ends. The sleeve also can be short enough to allow for bending of the flexor tendon through the pulley system of the hand. In a representative embodiment as used for repairing a flexor tendon, the length of the sleeve **12** can be about 0.340 inch, substantially greater than the maximum cross-sectional dimension. For smooth gliding, the shell wall should be as thin as possible, about 0.025 inch to 0.029 inch in a representative embodiment, and certainly much less than one-half the minor axis of the sleeve. The ends of the sleeve can be chamfered to ease sliding of the sleeve.

In the embodiment illustrated in FIGS. **1**, **2** and **3**, the severed end portions of the cord C are interconnected with the sleeve by pins **22** extending between the top and bottom walls of the sleeve. Several pins are provided at each side of the separation location L, preferably arranged in transversely extending rows. To prevent application of localized forces when the cord is under tension, pins of each row at each side of the separation location are staggered relative to the pins of an adjacent row. Also, it is preferred that the pins be of small diameter, approximately 0.023 inch to 0.032 inch in the representative embodiment, and at each side of the separation location the pins should be spaced apart a distance at least as great as the pin diameter. In the illustrated embodiment, the pins are provided in a 3-2-3 staggered configuration at each side.

Each pin **22** extends through aligned holes **24** and **26** in the top and bottom sleeve walls, respectively. As described below, the pins **22** can be driven through the aligned holes. Preferably, each pin has opposite end portions **28** of slightly reduced diameter as compared to the central portion of the pin extending through the tendon, such that narrow shoulders of the pins abut against the inner periphery of the shell to maintain the pins in position. The outer ends of the pins preferably are substantially flush with the outer periphery of the sleeve so that they will not snag or irritate adjacent tissue.

The top and bottom walls of the sleeve have aligned observation ports **30** large enough that the cord ends may be viewed so that the separation location L can be precisely positioned at the center of the sleeve. In the representative embodiment, the observation ports can be about 0.050 inch in diameter. At the sides, additional central observation ports **32** are provided, as well as smaller ports **33** toward the ends for the purpose of permitting synovial fluid to diffuse into and through the shell to promote healing. Similarly, as seen in FIG. **3**, the inner periphery of the shell can be provided with one or more V grooves **34** to allow blood flow to the cord. The sizes of ports **33** and groove **34** are not critical, except that care must be taken that the additional ports and groove(s) do not unduly weaken the sleeve.

With reference to FIG. **5** and FIG. **6**, each pin **22** can be molded of a suitable polymer with the reduced diameter end portions **28** forming the narrow, outward facing annular shoulders **36** for engaging against the inner periphery of the sleeve adjacent to the holes through the top and bottom sleeve walls. For ease of insertion of the pins through the tendon, each pin can be formed with a sharpened tip portion **38** projecting from one pin end portion **28**. A peripheral groove **40** can be formed between the sharpened tip portion **38** and the adjacent end portion **28** for ease in cutting away the tip portion after insertion of the pin so that the remaining pin end will be flush with the outer periphery of the sleeve.

Alternatively, the pin can be weakened sufficiently by the peripheral groove **40** that the tip portion can be broken off following insertion.

The modified pin **22'** shown in FIG. **7** and FIG. **8** is substantially identical to the pin **22** shown in FIGS. **5** and **6**, except that pin **22'** is provided with a separate stainless steel sharpened tip **38'** having a rear blind bore **42** for fitting on a corresponding cylindrical stud **43** molded integrally with the remainder of pin **22'**. The stainless steel tip can be press fitted to or otherwise secured to the stud **43**, such as by a suitable adhesive. In other respects, the pin of FIGS. **7** and **8** is identical to the pin previously described, including the peripheral groove **40** between the tip and the adjacent end portion **28**.

Testing was conducted with a prototype splice sleeve having the approximate dimensions given above, but with larger diameter pin holes and pins (approximately 0.033 inch) arranged in a 2-3 configuration at each side of the sleeve. Flexor tendons were harvested from fresh-frozen cadaveric hands. A tendon having a cross-sectional area approximately the same as the area encompassed by the inner periphery of the prototype sleeve was selected and severed using a surgical scalpel. The severed tendon end portions were fitted in the splice sleeve and secured with five pins at each side. The splice sleeve was formed of a polyimide polymer, nonbioabsorbable but similar in physical properties to bioabsorbable polydioxanone. One free end of the spliced tendon was clamped to a stationary block. The remaining free end was clamped to a low friction slide which, in turn, was secured to a cable. The cable was suspended over a single pulley and different weights then were secured to the hanging cable end to apply different tensile loads to the spliced tendon.

The spliced tendon remained in place at a tensile load of 46.9 Newtons (4.78 kilograms of vertical load) for 66 seconds at which time the testing structure, not the splice, failed. The splice, with the tendon and pins in place, was removed from the testing structure and examined. No evidence of failure was seen. The cut tendon ends remained visibly opposed within the observation portals, with no evidence of separation or gapping at the repair site. In contrast, similar testing was performed using flexor tendons "repaired" by suturing. The suture repair site showed signs of visible gapping upon application of 16.7 Newtons to 21.6 Newtons (1.70 to 2.20 kilograms of vertical load). The sutured repair failed immediately when tensile load was increased to 24.5 Newtons (2.50 kilograms of vertical load).

After repeat testing, some splitting of the tendon fibers adjacent to the connection pins was seen at higher forces. Consequently, it is preferred that the number of pins be increased and that the pin diameter be decreased to about 0.023 inch to 0.025 inch for a more uniform application of force throughout the repair site. The surprisingly strong forces that can be withstood without substantial separation of the abutting severed ends indicates that the splice can be used for connective cords stressed at higher loads than those normally applied to flexor tendons.

In the embodiment shown in FIGS. **9** and **10**, the modified sleeve **100** has a long integral hinge joint **102** along one side. The sleeve can be opened in clamshell fashion to the position shown in FIG. **9** for reception of the severed end portions of the cord. Thereafter the sleeve can be closed to the condition shown in FIG. **10**. The top and bottom portions of the sleeve have aligned holes **24** for pins **22**, **22'** of the type previously described. Preferably, a central observation port **30** is provided in at least the top of the sleeve. At the side opposite the hinge joint **102**, the sleeve has flanges **104** that abut when the sleeve is closed. The flanges can be stapled, clipped, sutured or otherwise secured together to maintain the sleeve in the closed position. Sleeve **100** has the same physical characteristics as the previously described embodiment. More than one longitudinally extending hinge joint can be used at the closed side of the sleeve.

Depending on the application, it may be desirable for the sleeve in accordance with the present invention to flex or bend for smooth excursion of the repaired cord. In the embodiment illustrated in FIG. **11**, the modified sleeve **110** has an array of openings **112** designed to enhance flexing or bending of the sleeve, without altering its rigidity in a longitudinal direction or its ability to rigidly anchor the connection pins. Stated in another way, although the sleeve can bend or flex, preferably it will not change its longitudinal dimension substantially which could alter the abutting relationship of the severed ends of the cord C, and preferably the transverse cross-sectional shape is not altered substantially. It is most important that the sleeve be able to bend or flex in the direction of its minor axis, i.e., up and down as viewed in FIG. **11**. The pattern of openings **112** can be selected to allow greater flexibility of the sleeve in that direction while minimizing longitudinal deflection. As for the previously described embodiments, the cord ends can be secured in the sleeve by pins **22** extending through aligned holes **24** in the top and bottom surfaces of the sleeve.

The embodiment illustrated in FIGS. **12** and **13** uses a reinforcement member or sleeve **130** having transversely extending slots **122** in the top and bottom. However, sleeve **130** has separate top and bottom pieces **132** and **134**, respectively. The top piece **132** and bottom piece **134** meet substantially contiguously at the sides along a scalloped border **136**. The cord ends can be held within the sleeve by horizontal pins extending transversely between aligned holes **24** in the opposite sides of the sleeve, and/or by sutures. In other respects, the sleeve is the same as previously described.

A clamshell embodiment of the present invention is shown in FIGS. **14** and **15**. Sleeve **160** has a bottom section **162** with an array of rigid pins **164** projecting vertically upward therefrom. Two side-by-side top sections **166** are provided, joined to the bottom section **162** by integral hinge joints **168**. The two top or "lid" sections **166** are spaced apart at the center of the sleeve. With the lids open, as illustrated in FIG. **14**, the cord end portions and sleeve are moved relative to each other for piercing the cord end portions and retaining them in position, with the cord ends abutting at approximately the center of the sleeve. Thereafter, the lids **166** can be closed. The lids have lock tabs **170** that fit over projections **172** along the adjacent edge of the bottom section of the sleeve. Pins **164** project through holes **176** in the top sections. When the lid sections have been closed, the projecting end portions of the pins can be cut flush with the exterior of the sleeve. Preferably, the pins are provided in transversely extending rows, with the pins of each row staggered relative to the pins of the most closely adjacent row, and with each pin spaced from the adjacent pins by an amount equal to at least the diameter of a pin.

In the embodiment shown in FIGS. **16–19**, the modified splice **200** in accordance with the present invention has separate top and bottom sections **202** and **204**, respectively. The bottom section has straight rigid pins **206** projecting upward therefrom in alignment with transverse slots **208** through the top section. Similarly, the top section **202** has pins **210** projecting downward in alignment with transverse slots **212** of the bottom section. When the top and bottom

sections are brought together, the free end portions of the pins fit in the slots of the other section, as best seen in FIG. **18**. This helps to assure that the pins are held firmly in a vertical position without deflecting. The projecting sharpened tips of the pins can be cut flush with the periphery of the sleeve.

In addition, the bottom section has an undercut shoulder **214** extending lengthwise along its upper edge portions, to mate with a corresponding lip **216** of the top section. The lip **216** interfits with the undercut shoulder portion as best seen in FIG. **19** for holding the top and bottom sections together after the severed cord ends have been secured in position.

The embodiment illustrated in FIG. **20** has separate collars **242'** secured to the severed cord end portions, respectively, such as by suturing or rigid pins extending through opposing faces. One collar **242'** (the collar at the top in FIG. **20**) has transversely spaced bosses **252** at the top and bottom. Flexible line or rail members **254** extend from bosses **252**, and through aligned holes in the bosses **256** of the other collar. After the severed end portions of the cord are affixed in their respective collars, the collars are brought together and held in position by tying off the projecting free end portions of the rails or by otherwise fixing the rails in the bosses **256** through which they otherwise would slide. Preferably the bosses **252,256** would have a lower profile and be a smooth transition from the periphery of the associated collar.

The embodiment of the present invention illustrated in FIGS. **21** and **22** uses a composite sleeve **270** having two separate end collars **272** and **274** spaced apart by a center collar **276**. The adjacent ends of adjacent collars can have matching undulating edges **278** including, for example, central humps or nose portions **280** on collars **272** and **276** received in central depressions or valleys **282** of collars **276** and **274**, respectively. The separate collars are connected together by links **284** which permit limited resilient flexing of the collars relative to each other, particularly in the direction of the minor axis of the composite sleeve. The inner periphery of the sleeve preferably is smooth with no internal projections which would hinder fitting of the collars on the severed end portions of a damaged connective cord.

Links **284** can be formed integrally with connection pins **286** that project perpendicularly downward therefrom. Holes **288** are provided in the tops and bottoms of adjacent collars, with recesses **290** at the top sized to receive the links. When the pins are inserted downward through a cord, the tops of the links lie flush with the remainder of the periphery of the composite sleeve **270**. The bottom ends of the pins can be sharpened and include necks **292** of reduced diameter for snapping into the holes **288** in the bottom surfaces of the collars. Any projecting portions of the sharpened tips at the bottom can be cut off. At least the upper portion of the middle collar **276** can have observation ports **297** for viewing the abutting end portions of the damaged cord to assure that they abut prior to insertion of the pins.

With reference to FIG. **22**, the links **284** bridge between adjacent collars, such as collars **274** and **276**, and can be dimensioned to space the collars apart slightly, so as not to inhibit the flexing movement of one collar relative to another. In addition, the bridging portions of the links can have weakening grooves **294** which assist in permitting the flexing movement, preferably without introducing a tendency of the links to expand or contract lengthwise. For example, it still is preferred that the length of the composite sleeve **270** not increase or decrease substantially due to forces applied to the repaired cord. In addition, limited sideways flexing of the sleeve (in the direction of the major cross-sectional axis) can be permitted by tapering the depressions **290**.

The embodiment illustrated in FIGS. **23** and **24**, similar to the embodiment shown in FIGS. **21** and **22**, uses a multi-part composite sleeve **300** including end collars **302** and **304** spaced apart by a middle collar **306**. As for the embodiment of FIG. **21** and FIG. **22**, the collars have identical cross sections and are aligned lengthwise of the centerline of the sleeve. Separate pins can be provided for extending through registered holes in the tops and bottoms for securing the collars to the damaged cord to be repaired. In the embodiment illustrated in FIGS. **23** and **24**, three rigid pins **308** are provided for each of the two end collars **302** and **304**, joined at the top by flush bridging portions **310**. The middle section has two pairs of pins **312**, each pair forming a transversely extending row with its pins staggered relative to the pins of the end collars. The pins of each pair can be connected by a flush bridging portion **314**. The pairs of pins **312** are arranged at opposite sides of the center of the sleeve such that each pair penetrates a different severed end portion of the damaged cord.

To allow flexing of the sleeve in the direction of its minor axis, connecting links **316** are provided at each side. One end of each link is pivotally connected to an end collar, and the other end of each link **316** is pivoted to the center collar **306**. As seen in FIG. **24**, the links are received in tapered recesses **318** which allow limited swinging of the links relative to the collars to which they are connected. The pivotal connection can be achieved by inward projecting buttons of the links being snap fitted in corresponding holes of the collars.

FIGS. **25–28** show another type of rigid or semi-rigid reinforcement member **400** used to repair soft tissue T, as illustrated in FIG. **26**, where a tendon is severed at location L. The reinforcement member **400** is a flat band inserted lengthwise into first one and then the other of the severed cord (tendon) ends. The band preferably has sharpened ends **402**. In the embodiment illustrated in FIGS. **25–28**, the band is of substantially uniform width and thickness except for the sharpened ends, and has a series of through holes **404** aligned lengthwise of the band. Alternatively, smaller diameter holes **404'** can be provided, including two holes in a transversely extending row, one at each side of the longitudinal centerline of the reinforcement member or band **400**, and a third hole spaced longitudinally of the band from the first two holes and located approximately on the centerline.

The reinforcement member or band **400** can be secured to the tissue T by transversely extending pin assemblies **406**, the details of which are seen in FIGS. **27** and **28**. Each pin assembly **406** includes a first pin component having an enlarged head **408** and a shank **410** of a size for fitting closely in the holes **404** or **404'**. The pins are firmly enclosed in and positioned by the snug engagement in the holes of the reinforcing member so as not to deflect or bend longitudinally of the cord when tension is applied. A second component includes a ring or collar **412** adapted to be fitted over the end of the shank **410** opposite the enlarged head **408**. Collar **412** is of approximately the same diameter as the enlarged head **408**, i.e., substantially greater than the reduced diameter shank **410** of the pin assembly. The smaller end of the shank adjacent to the collar can be crimped or otherwise upset to retain the collar in position.

As seen in FIGS. **27** and **28**, the enlarged heads **408** and collars **412** of the pin assemblies can be sized and crimped for compressing the tissue being repaired. In the case of a tendon, the enlarged heads of the pin assemblies are inti-

mately engaged with the epitenon. This is believed to be important if the repaired tendon is to withstand substantial tensional forces while healing. For example, mechanical strength tests were performed on sheep tendon with and without the epitenon, by piercing the tendon diametrally with a single 0.020 inch diameter steel pin and applying force to the pin axially of the tendon. The ultimate pullout strength of the pin was decreased by about 50% when the epitenon was removed—about 30 Newtons with the epitenon intact and about 15 Newtons with the epitenon removed. To further increase the pullout force, pins corresponding to the smaller diameter, staggered holes **404'** (FIG. **25**) can be used, which has the effect of spreading the tensional forces more uniformly throughout the cross-section of the tendon.

In the embodiment of FIGS. **29–32**, an internal reinforcement member **450** has a narrow central portion **452** and wider opposite end portions **454** with sharpened ends **456**. The wider end portions have holes **458** or **458'** to receive the pin assemblies **416**. The narrow central portion **452** of the device connecting the enlarged ends is thicker than the ends, as seen in FIG. **31**, and such central portion has a short central disc projection **460**. The thicker center and central disc are positioned adjacent to the severed ends of the tissue or cord T. The disc **460** and thicker central portion **452** help to maintain the ends in alignment by flexing to a lesser degree than the end portions **454**, such as during normal excursion of the tendon following the repair.

The embodiment shown in FIGS. **33** and **34** uses an internal reinforcement member **500** of the general type previously described, preferably with two holes **502** at each end of the device. The holes of each pair are offset relative to the longitudinal centerline. At each end, two thin (approximately 0.008 inch thick) flat band sleeves **504** wrap around the outside of the tendon and act to constrain it. Pins **506** having sharpened ends **508** and enlarged heads **510** pass through the sleeves **504**, then through the holes **502**, and finally through the opposite sides of the sleeves. The dimensions are exaggerated in FIGS. **33** and **34**, preferably the pins would not have abruptly projecting ends, particularly in the case of tendon repair. Rather, the ends would be smoothly contoured into the sleeves, with the sleeves depressed into the epitenon so as not to unduly interfere with excursion of the tendon during healing. Tension applied to one cord end is transmitted generally from one sleeve and associated set of pins, through the reinforcement member, and through the other set of pins and associated sleeve to the opposite cord end.

While the preferred embodiment of the invention has been illustrated and described, it will be appreciated that various changes can be made therein without departing from the spirit and scope of the invention.

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. A splice for repair of a severed connective cord normally tensioned in the body during joint movement, said splice comprising a reinforcing member of substantially rigid or semirigid material, said member being adapted for extending longitudinally between severed end portions of a connective cord with the severed end portions in abutting relationship, and means for securing the cord to the reinforcing member such that tension applied to the cord is transmitted through the reinforcing member and for maintaining the severed ends abutting as tension is applied to the cord by transmitting tensional force through the reinforcing member, the securing means including a plurality of pins anchored in the reinforcing member and extending at least part way through the connective cord for transmission of tensional force from the connective cord through the pins and the reinforcing member.

2. The splice defined in claim **1**, in which the reinforcing member includes a hollow sleeve sized to closely receive the adjacent end portions of the severed cord.

3. The splice defined in claim **1**, in which the reinforcing member is elongated and adapted for extending internally of the abutting severed cord end portions.

4. The splice defined in claim **3**, in which the pins extend oppositely from the reinforcing member, transversely of the connective cord.

5. The splice defined in claim **3**, in which the securing means includes at least one sleeve component adapted to encircle the cord, the pins being adapted to extend through the sleeve component and the reinforcing member.

6. The splice defined in claim **5**, in which the pins have opposite ends adapted to be embedded in opposite sides of the sleeve compartment.

7. The splice defined in claim **1**, in which the securing means includes a plurality of pins extending through each of the abutting end portions of the severed cord.

8. The splice defined in claim **7**, in which the pins extending through each of the abutting end portions of the severed cord include pins which are offset from each other.

9. The splice defined in claim **7**, in which the pins extending through each of the adjacent ends of the severed cord are arranged such that tension applied to the cord is transmitted substantially uniformly throughout the cross section of the cord.

10. The splice defined in claim **1**, in which the pins are anchored in the reinforcement member so as not to flex or deflect in a direction longitudinally of the cord.

11. The splice defined in claim **1**, in which the reinforcement member is adapted to flex transversely of the length of the cord without substantial change in the length of the reinforcement member while still maintaining the adjacent ends of the severed cord in abutting relationship.

12. The splice defined in claim **11**, in which the reinforcement member is constructed so as to be less flexible in the area bridging between the abutting ends of the severed cord than at locations farther from the adjacent ends of the severed cord.

13. The splice defined in claim **1**, in which the securing means includes a plurality of rigid pins arranged in rows with the pins of one row offset from the pins of an adjacent row.

14. The splice defined in claim **1**, in which the pins are of a diameter no greater than about 0.025 inch.

15. The splice defined in claim **1**, in which the pins have enlarged heads at their opposite end portions adapted to engage the epitenon of a severed tendon.

16. The splice defined in claim **15**, in which the enlarged heads of the pins are adapted to compress into the epitenon.

17. The splice defined in claim **1**, in which the pins have opposite ends adapted to be substantially flush with the outer periphery of the connective cord.

18. The splice defined in claim **1**, in which the pins are provided in multiple pieces including an elongated shank having an enlarged collar adapted to interfit with the sharpened end.

19. The splice defined in claim **1**, in which the reinforcing member is formed of bioabsorbable material.

20. The splice defined in claim **19**, in which the splice is formed of bioabsorbable material selected to absorb into the body over a preselected period of time but at a rate no greater than the rate of healing of the cord such that at each stage of

healing the combined strength of the splice and the healing cord is at least equal to the maximum force to which the cord is normally subjected.

21. The splice defined in claim 1, in which the reinforcing member has a plurality of preformed holes, the securing means including pins having shanks of predetermined cross-sectional shape and size for tightly fitting in the preformed holes of the reinforcing member.

22. The splice defined in claim 1, in which the reinforcing member includes a first component adapted to bridge between the adjacent ends of the severed connective cord, a second component adapted to overly the exterior of one of the adjacent ends of the severed cord, a third component adapted to overly the other of the adjacent ends of the severed connective cord, and a plurality of pins for connecting, respectively, the second and third components with the first component.

23. A splice for repair of a severed connective cord normally tensioned in the body during joint movement, said splice comprising a reinforcing member of substantially rigid or semirigid material, said member being adapted for extending longitudinally between severed end portions of a connective cord with the severed end portions in abutting relationship, and means for securing the cord to the reinforcing member such that tension applied to the cord is transmitted through the reinforcing member and for maintaining the severed ends abutting as tension is applied to the cord by transmitting tensional force through the reinforcing member, the splice being formed of bioabsorbable material selected to absorb into the body over a preselected period of time but at a rate no greater than the rate of healing of the cord such that at each stage of healing the combined strength of the splice and the healing cord is at least equal to the maximum force to which the cord is normally subjected.

* * * * *

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United States Patent [19]

Pauley et al.

[11] **Patent Number: 6,060,640**

[45] **Date of Patent: May 9, 2000**

[54] **MULTIPLE-LAYER, FORMED-IN-PLACE IMMUNOISOLATION MEMBRANE STRUCTURES FOR IMPLANTATION OF CELLS IN HOST TISSUE**

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[73] Assignee: **Baxter International Inc.**, Deerfield, Ill.

[21] Appl. No.: **08/446,210**

[22] Filed: **May 19, 1995**

[51] **Int. Cl.**[7] **A61F 2/02**; C12N 5/08; A61M 31/00; A61D 7/00

[52] **U.S. Cl.** **623/11**; 623/1; 623/2; 623/3; 623/12; 623/13; 623/16; 623/18; 623/66

[58] **Field of Search** 623/1, 2, 3, 10, 623/11, 12, 16, 18, 66

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Primary Examiner—Mickey Yu
Assistant Examiner—Choon P. Koh
Attorney, Agent, or Firm—McDonnell, Boehnen Hulbert & Berghoff

[57] **ABSTRACT**

A permeable structure forms a chamber to hold living cells. The structure includes a first permeable region surrounding at least a portion of the chamber having a conformation that, when implanted in host tissue, substantially blocks penetration of host cells into the chamber while permitting solute transport. The structure also includes a second permeable region overlying the first permeable region having a conformation that, when implanted in host tissue, forms a permeable interface with host tissue that permits solute transport. A third permeable region is located between the first and second permeable regions. The third region comprises a solution of polymer material formed in place between the first and second permeable regions. The third permeable region bonds the first and second permeable regions together. The third permeable region also has a conformation that, when implanted in host tissue, permits solute transport between the first and second permeable regions. The third, formed-in-place region bonds the first and second permeable regions together, providing a robust, laminated structure that resists delamination during implantation caused by cellular infiltration into discontinuous spaces between the first and second regions. The third, formed-in-place region can also have a conformation providing an immunoisolation effect. Furthermore, the permeability of the third, formed-in-place membrane is sufficient high that it does not adversely effect the permeability value desired for the overall multiple layer membrane structure.

32 Claims, 13 Drawing Sheets

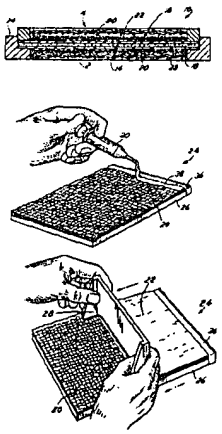

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FIG. 1

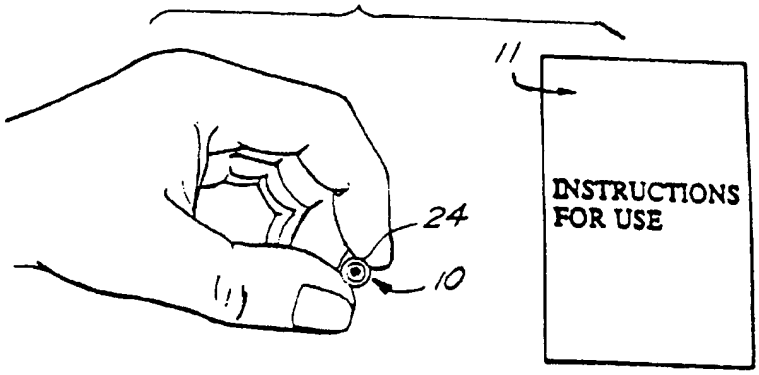


FIG. 2

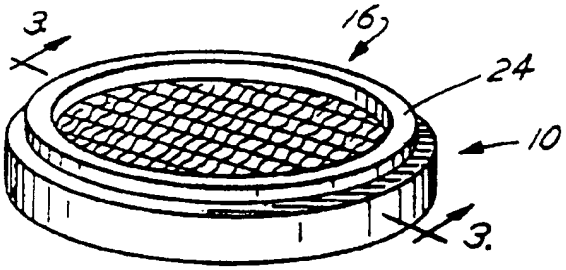


FIG. 3

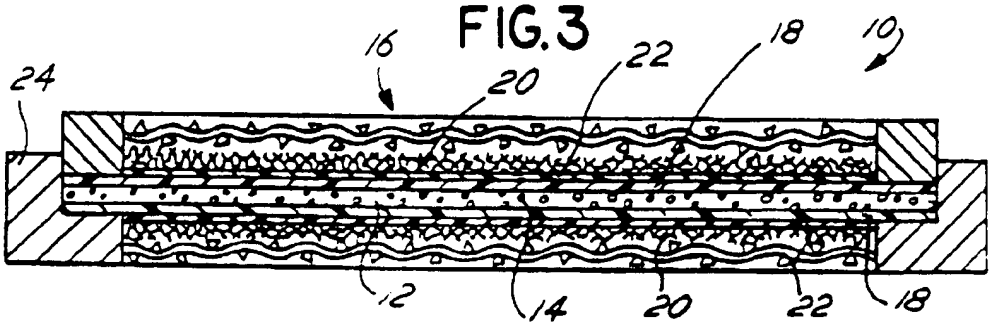


FIG. 2A

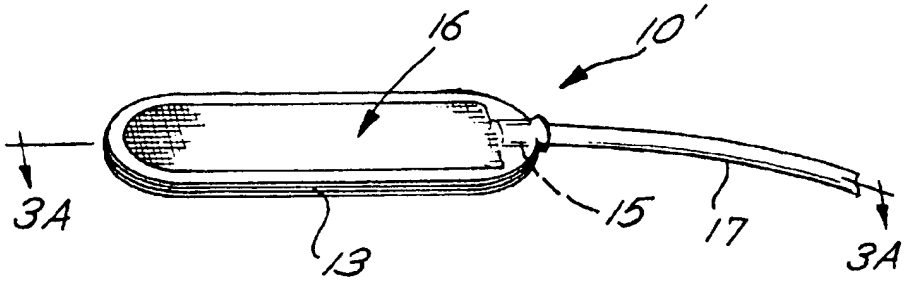


FIG. 3A

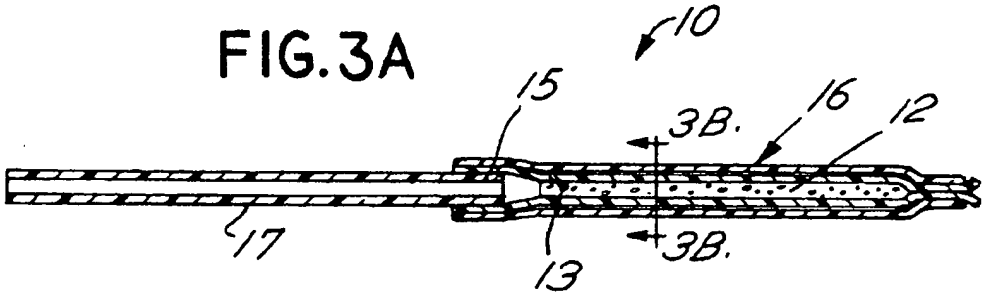
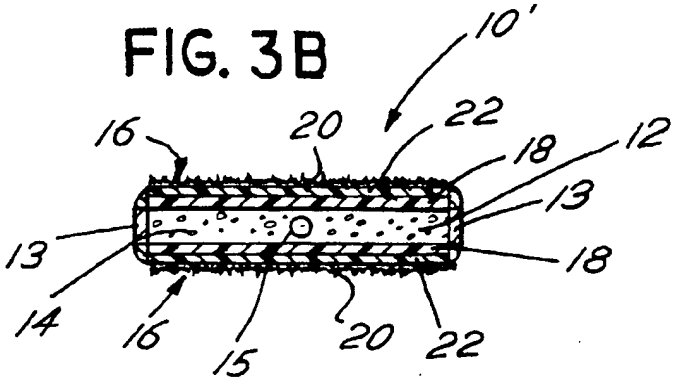


FIG. 3B



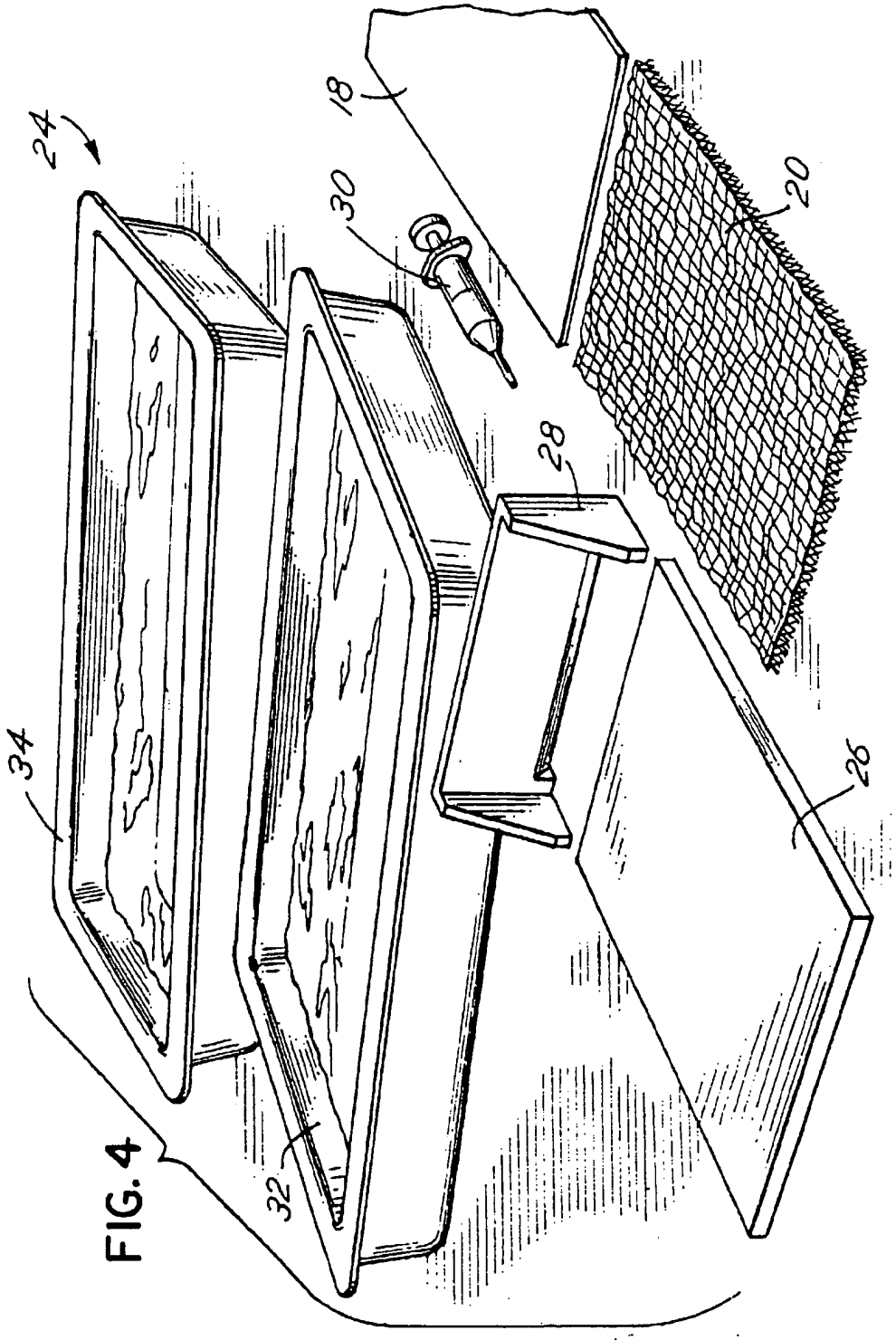


FIG. 4

FIG. 5

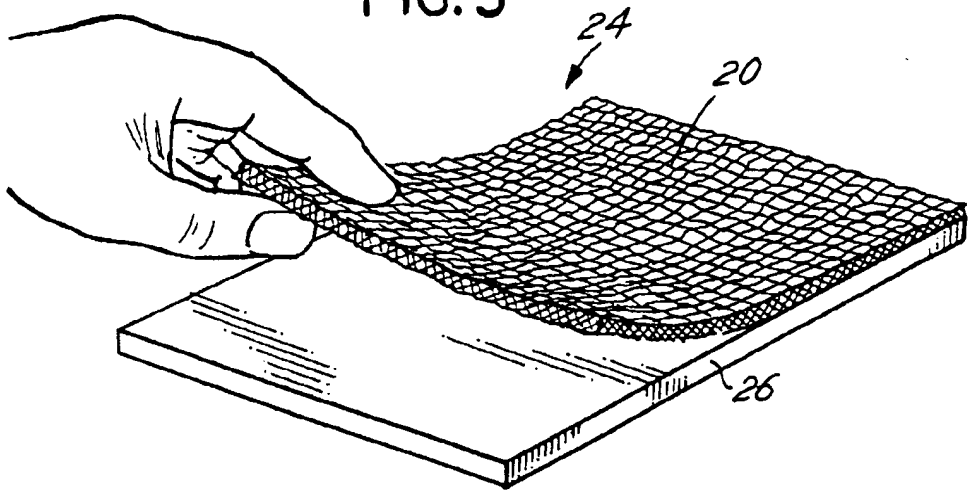
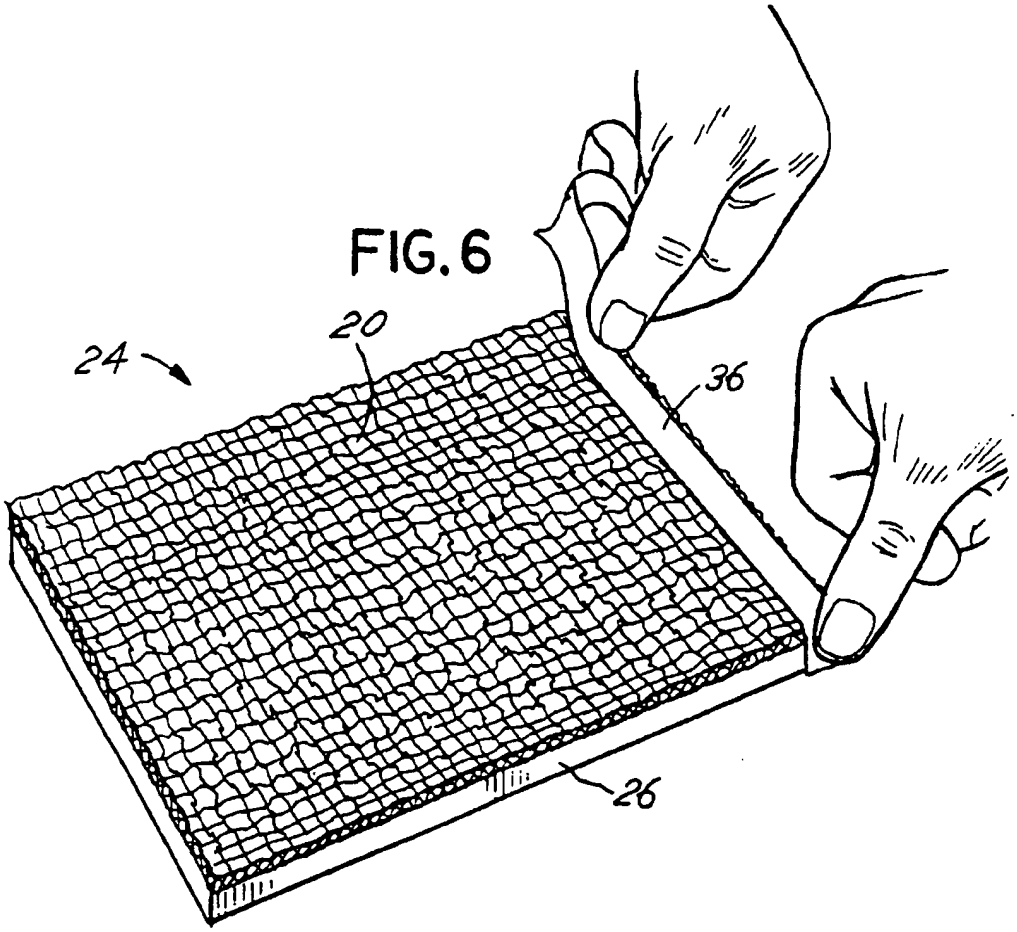


FIG. 6



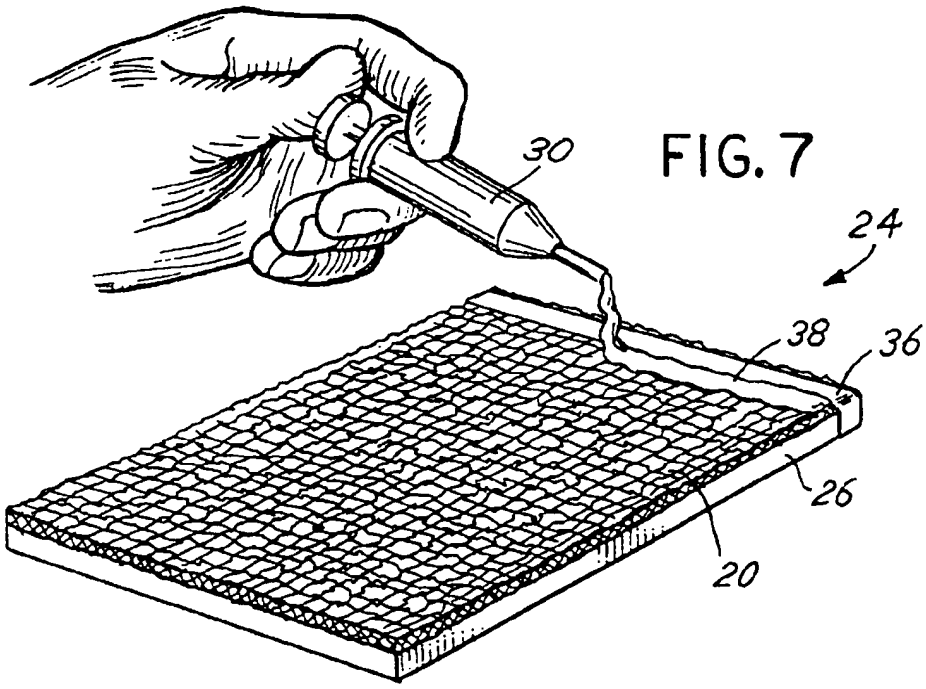


FIG. 7

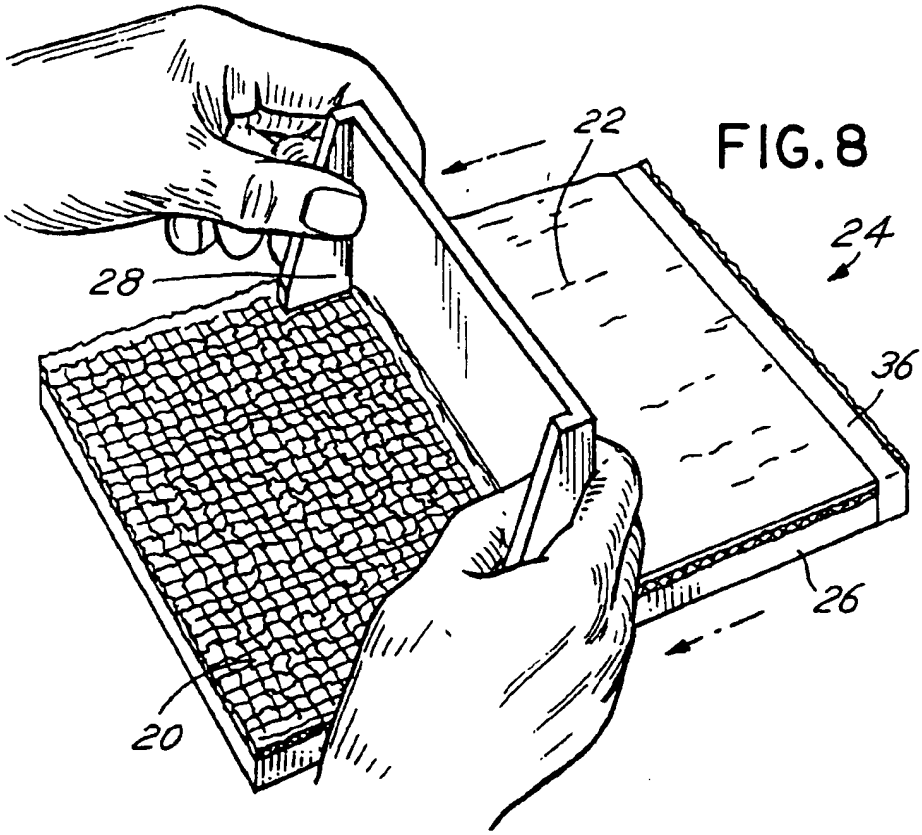


FIG. 8

FIG.9

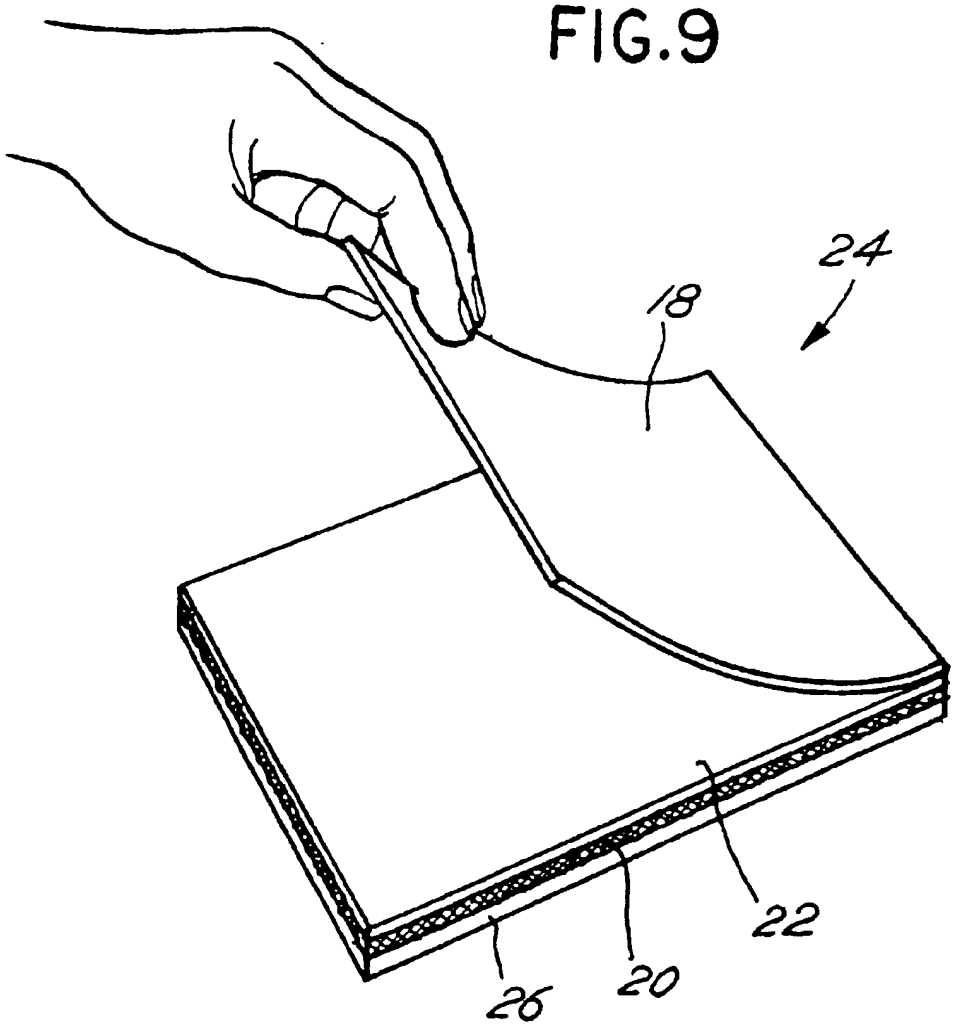
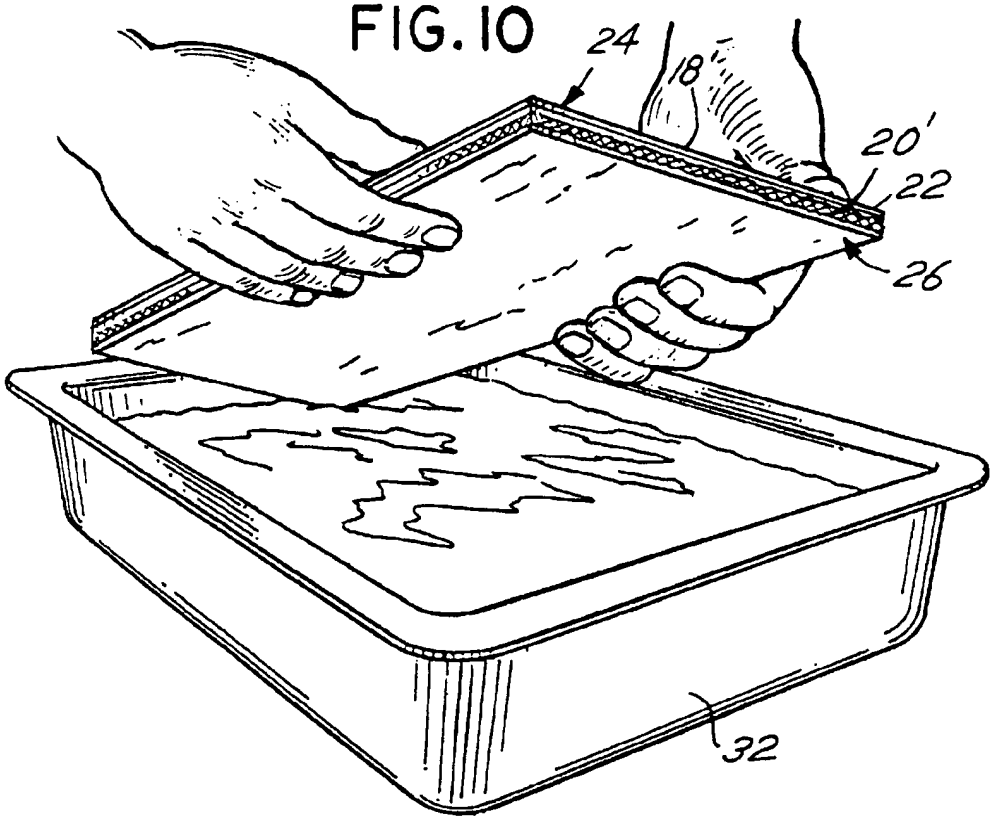


FIG. 10



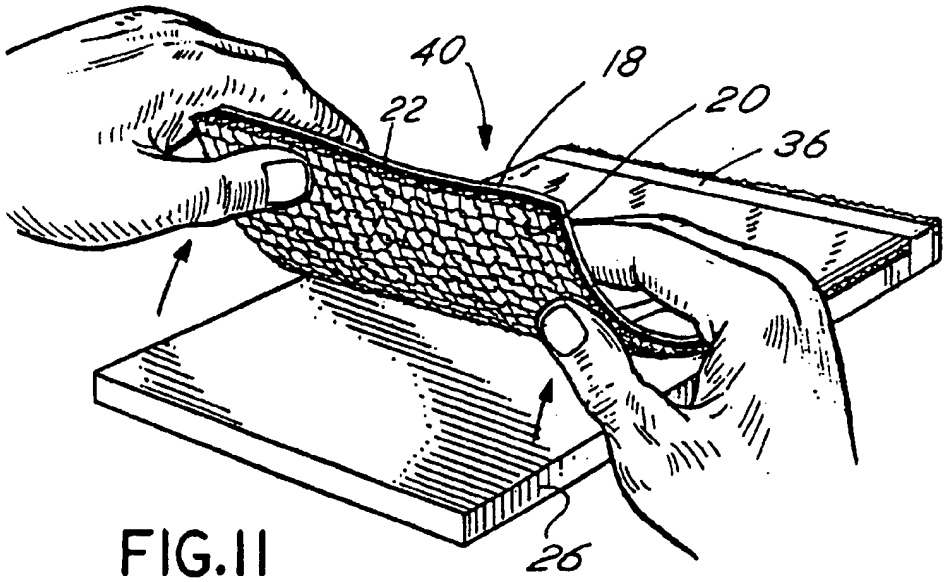


FIG. 11

FIG. 12

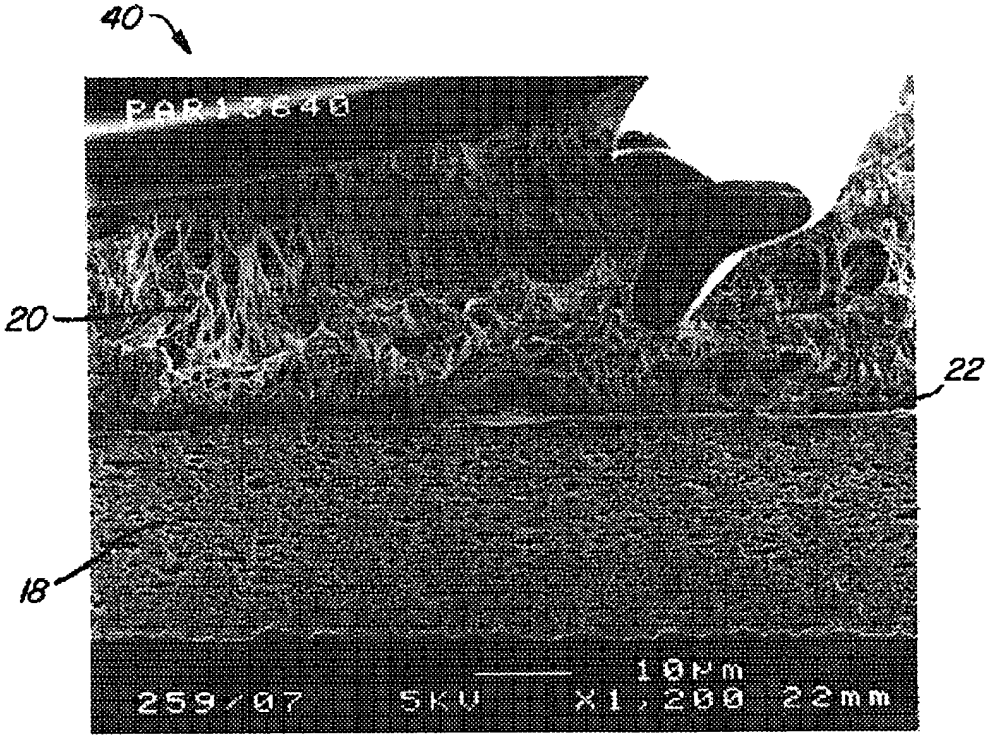


FIG. 13

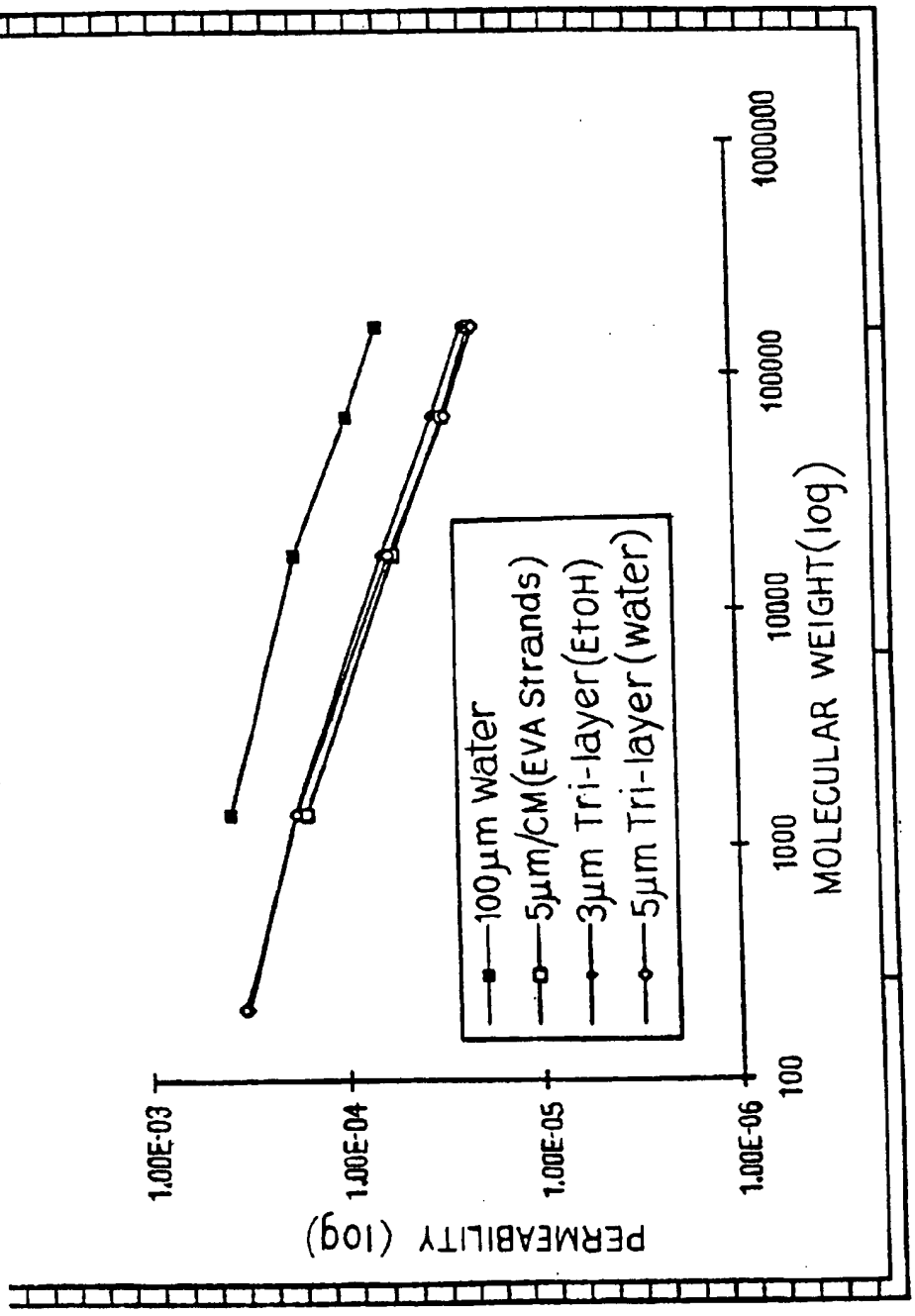

PERMEABILITY (log)
1.00E-03
1.00E-04
1.00E-05
1.00E-06
100
1000
10000
100000
1000000
MOLECULAR WEIGHT(log)
100μm Water
5μm/cm(EVA Strands)
3μm Tri-layer(EtOH)
5μm Tri-layer(water)

FIG. 14

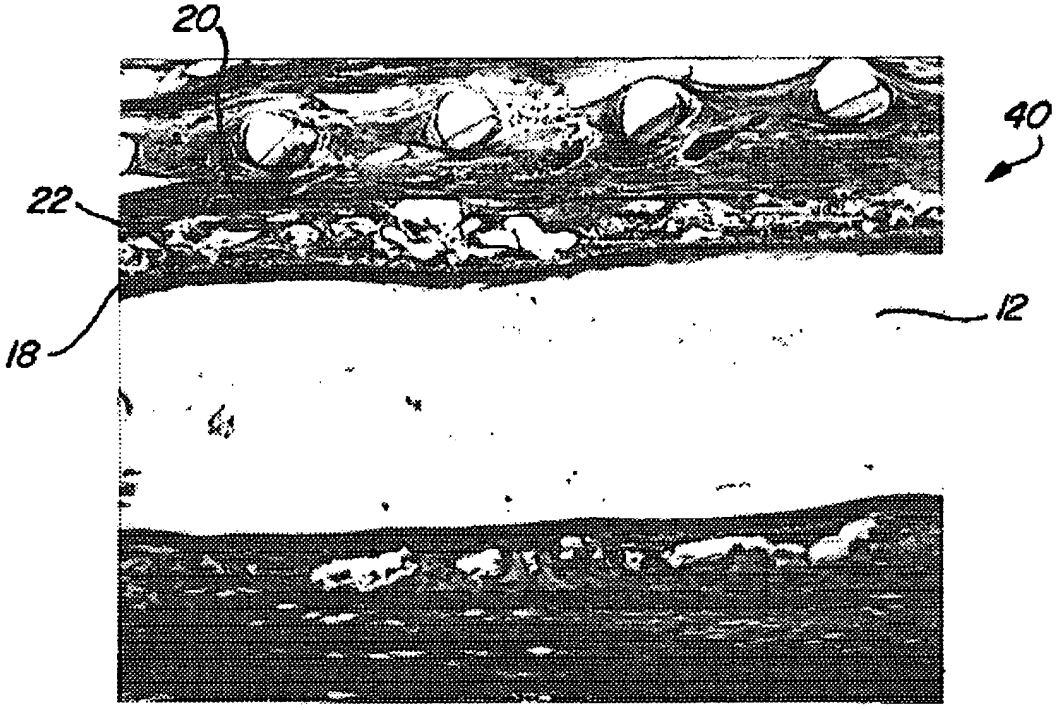


FIG. 15

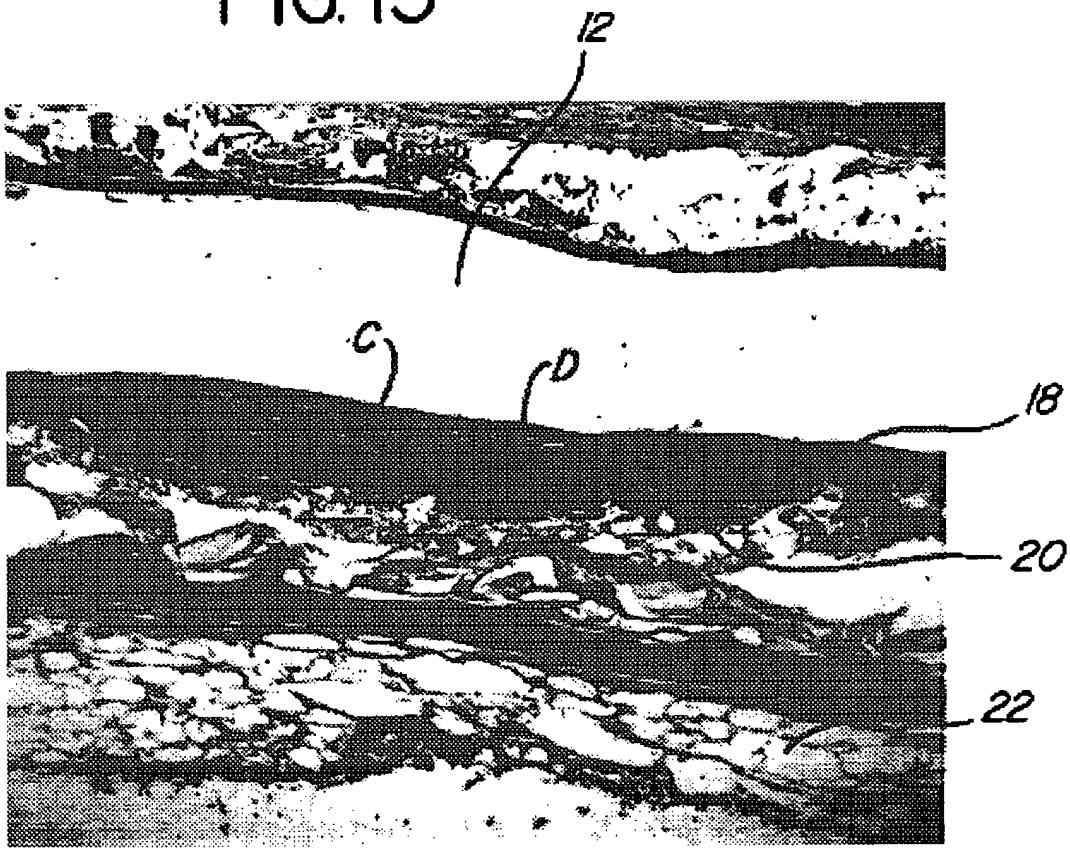


FIG. 16

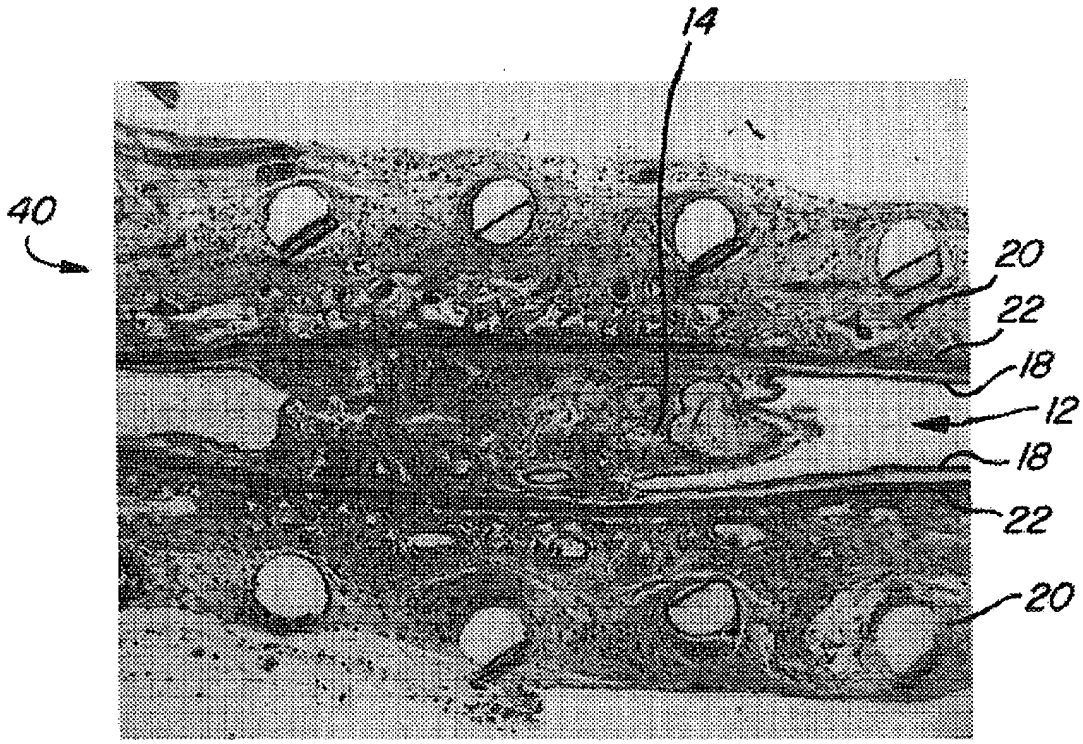
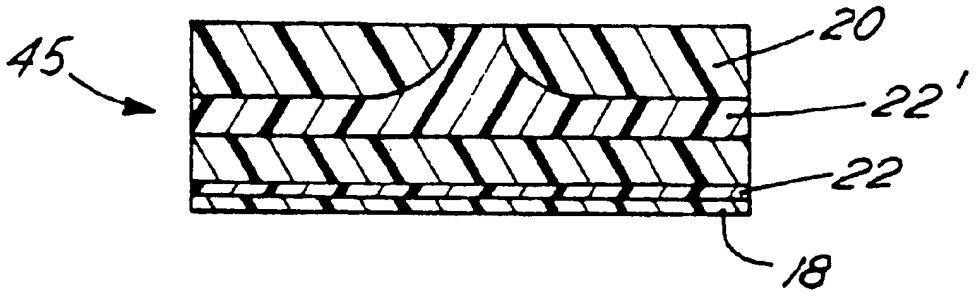


FIG.17



MULTIPLE-LAYER, FORMED-IN-PLACE IMMUNOISOLATION MEMBRANE STRUCTURES FOR IMPLANTATION OF CELLS IN HOST TISSUE

FIELD OF THE INVENTION

The invention generally relates to systems and methods for implanting materials into body tissue. In a more particular sense, the invention relates to the structures and methods for implanting living cells in host tissue within permeable membrane structures for achieving a desired therapeutic effect, such as, for example, the treatment of diabetes.

BACKGROUND OF THE INVENTION

Many diseases could be treated in a more physiologic fashion if tissue from lower animals could be transplanted into humans. Immunoisolation, as its name implies, is the protection of transplanted organs, tissues, cells, etc. from attack by the host immune system. Isolation from the host immune system is accomplished by the use of a semipermeable membrane.

Recent work by Brauker et al. has demonstrated that a prescribed membrane architecture can promote vascular structures near the host tissue-membrane interface. Such membranes had pores that were formed by membrane structures (strands or fibers) with a diameter of less than 5 μm, whereas membranes that did not develop near vascular structures had cavities with "plate-like" qualities, having diameters greater than 5 μm. Histological examination of the vascularizing membranes revealed that the invading inflammatory cells (of the host) had a rounded morphology, while the cells were flattened in the membranes that did not have close vascular structures. See, Brauker et al., Neovascularization of Synthetic Membranes Directed by Membrane Microarchitecture, J. Biomed. Mat. Res., In Press; Brauker, J., Martinson, L., Young, S., Johnson, R. C.: Neovascularization at a membrane-tissue interface is dependent on microarchitecture. Transactions of the Fourth World Biomaterials Congress Apr. 24–28, 1992 p. 685; Brauker, J., Martinson, L., Carr-Brendel, V. E., and Johnson, R. C.: Neovascularization of a PTFE membrane for use as the outer layer of an immunoisolation device. Transactions of the Fourth World Biomaterials Congress Apr. 24–28, 1992 p. 676; Brauker, J., Martinson, L., Hill, R., and Young, S.: Neovascularization of immunoisolation membranes: The effect of membrane architecture and encapsulated tissue. Transplantation 1:163,1992; and Brauker, J., Martinson, L. A., Hill, R. S., Young, S. K., Carr-Brendel, V. E., and Johnson, R. C.: Neovascularization of immunoisolation membranes: The effect of membrane architecture and encapsulated tissue. Transplantation Proceedings 24:2924, 1992; copending Brauker et al. U.S. patent application Ser. No. 08/210,068, filed Mar. 17, 1994, entitled "Close Vascularization Implant Material."

Membranes of the type characterized by Brauker et al. facilitate high levels of vascularization near the membrane-host tissue interface.

Vascularization-promoting membranes of the type characterized by Brauker at el. still must be used in association with an immunoisolation membrane. The immunoisolation membrane is placed between the vascularization membrane and the implanted tissue and has a pore size sufficient to block penetration by host vascular structures completely through the permeable boundary that separates the implanted cells from host tissue. Such penetration breaches the integrity of the boundary , exposing the implanted cells

to the complete immune response of the host. Furthermore, the immunoisolation membrane must also prevent the passage of host inflammatory cells (in the case of allografts) and the passage of both host inflammatory cells and molecular immunogenic cells (in the case of xenografts). Vascularization-promoting membranes of the type characterized by Brauker et al., when used in association with an immunoisolation membrane, are capable of supporting allografts at high tissue densities for extended periods, even in the absence of immunosuppressive drugs.

The need for both a vascularization-promoting membrane and an immunoisolation membrane has resulted in laminated membrane structures. For example, Clarke et al U.S. Pat. No. 5,344,454 discloses the lamination of a GORE-TEX™ membrane material (which serves as a vascularization-promoting membrane) and a BIOPORE™ membrane material (which serves as an immunoisolation membrane for allografts) using a criss-crossing pattern of nonpermeable polymeric adhesive. It has been observed that this laminated structure can experience delamination when implanted. This delamination is caused by the infiltration of host inflammatory cells between the two membrane materials, forcing the material apart. This delamination can increase the diffusion distance the laminated membrane structure presents between the host vascular structures and implanted tissue. This, in turn, can adversely effect the passage of nutrients through the laminated membrane structure to the implanted cells.

SUMMARY OF THE INVENTION

One aspect of the invention provides a permeable multiple layer, laminated structure for implanting in host tissue. The permeable structure forms a chamber to hold living cells. The structure includes a first permeable region surrounding at least a portion of the chamber having a conformation that, when implanted in host tissue, substantially blocks penetration of host cells into the chamber while permitting solute transport. The structure also includes a second permeable region overlying the first permeable region having a conformation that, when implanted in host tissue, forms a permeable interface with host tissue that permits solute transport. According to this aspect of the invention, a third permeable region is located between the first and second permeable regions. The third region comprises a solution of polymer material formed in place between the first and second permeable regions. The third permeable region bonds the first and second permeable regions together. The third permeable region also has a conformation that, when implanted in host tissue, permits solute transport between the first and second permeable regions.

The third, formed-in-place region bonds the first and second permeable regions together, providing a robust, laminated structure that resists delamination during implantation caused by cellular infiltration into discontinuous spaces between the first and second regions. The third, formed-in-place region can also have a conformation providing an immunoisolation effect. Furthermore, the permeability of the third, formed-in-place membrane is sufficient high that it does not adversely effect the permeability value desired for the overall multiple layer membrane structure.

Another aspect of the invention provides a permeable structure with a redundant immunoisolation barrier. The structure includes a permeable layer surrounding the chamber that, when implanted in host tissue, blocks contact between cells in the chamber and host cells while permitting transport of solutes. The permeable layer includes a first immunoisolation region having a conformation that, when

implanted in host tissue, substantially blocks penetration of host inflammatory cells. The permeable layer also includes a second immunoisolation region distinct from the first region. The second region has a conformation that, when implanted in host tissue, also substantially blocks penetration of host inflammatory cells. The first and second regions are mutually arranged in the permeable layer to together provide a redundant immunoisolation barrier.

In one embodiment, the first and second immunoisolation regions contact each other in the layer. In another embodiment, the first and second immunoisolation regions are spaced apart in the layer.

In a preferred embodiment, the first immunoisolation region is formed in place in contact with the second immunoisolation region by being cast in contact with the second immunoisolation region and then coagulated in place in contact with the second immunoisolation region.

The invention also provides methods for making devices for implanting in host tissue using the permeable structure, as well as methods for implanting living cells within such devices in host tissue.

Other features and advantages of the inventions will become apparent upon review of the following specification, drawings, and claims.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a perspective view of an implant assembly that includes a formed-in-place laminated membrane structure that embodies features of the invention, being held in a clinician's hand;

FIG. **2** is an enlarged perspective view of the implant assembly shown in FIG. **1**;

FIG. **2A** is an enlarged perspective view of an alternative implant assembly that includes a formed-in-place laminated membrane structure that embodies features of the invention;

FIG. **3** is a side section view of the implant assembly with formed-in-place laminated membrane structure, taken generally along line **3**—**3** in FIG. **2**;

FIG. **3A** is a side section view of the assembly shown in FIG. **2A** taken generally along line **3A**—**3A** in FIG. **2A**;

FIG. **3B** is an enlarged end section view of the assembly shown in FIG. **2A**, taken generally along line **3B**—**3B** in FIG. **3A**;

FIG. **4** is a perspective view of a casting chamber containing apparatus used to manufacture formed-in-place laminated membrane structures that embody features of the invention;

FIGS. **5** to **11** show the steps in manufacturing the formed-in-place laminated membrane structure using the apparatus shown in FIG. **4**;

FIG. **12** is a micrograph of a formed-in-place laminated membrane structure that embodies the features of the invention;

FIG. **13** is a log graph comparing the permeability of formed-in-place laminated membrane structures embodying the invention to a prior laminated membrane structure;

FIG. **14** is a micrograph of a formed-in-place laminated membrane structure after implantation in host dog tissue for ten weeks, showing the absence of delamination;

FIG. **15** is a micrograph of a prior laminated membrane structure after implantation in host dog tissue for ten weeks, showing the presence of delamination;

FIG. **16** is a micrograph of a formed-in-place laminated membrane structure after implantation in host rat tissue for three weeks, showing the absence of delamination; and

FIG. **17** is a side section view of a redundant immunoisolation barrier that embodies the features of the invention.

The invention may be embodied in several forms without departing from its spirit or essential characteristics. The scope of the invention is defined in the appended claims, rather than in the specific description preceding them. All embodiments that fall within the meaning and range of equivalency of the claims are therefore intended to be embraced by the claims.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

I. The Implant Assembly

FIGS. **1** to **3** show one embodiment of an implant assembly **10** that embodies the features of the invention. FIGS. **2A** and **3A/B** show an alternative embodiment of such an implant assembly **10'**, which represents a preferred embodiment for reasons set forth below.

Both assemblies **10** and **10'** form a chamber **12** (see FIGS. **3** and **3A/B**) to hold living cells **14** while implanted in host tissue. The implanted cells **14** generate biological products that the host, because of disease or injury, cannot produce for itself. For example, the chamber **12** can carry clusters of pancreatic cells (called "islets"), which generate insulin for release into and use by a diabetic host.

In the embodiment shown in FIG. **2**, the assembly **10** is carried within a hoop-like housing **24**. The details of construction of the hoop-like housing **24** are disclosed in U.S. Pat. No. 5,344,454, which is incorporated herein by reference. In the embodiment shown in FIGS. **2A** and **3A/13**, the assembly **10'** comprises a peripherally welded unit, without need for an external housing to lend mechanical support.

The assemblies **10** and **10'** each forms a permeable, life sustaining boundary **16** between the implanted cells **14** and the host. The permeable boundary **16** is characterized in terms of its ultimate physical strength and its permeability profile. The boundary **16** serves to isolate the implanted tissue cells from the immune response of the host. The boundary **16** also serves to transfer nutrients and waste products in support of the metabolic processes of implanted cells. The assembly **10'** shown in FIGS. **2A** and **3A/B** includes a sealing or spacing ring **13**, to which the peripheral edges of the boundary **16** are sealed by ultrasonic welding.

Regardless of whether the implanted cells **14** are xenogeneic, allogeneic, or isogeneic, the boundary **16** possesses an ultimate strength value that is sufficient to withstand, without rupture, the growth of new vascular structures, the growth of new cells within the chamber **12**, and other physiological stresses close to the host tissue. Keeping the boundary **16** secure assures isolation of the implanted cells from both the immunogenic factors and inflammatory cells of the host.

These physiological stresses are caused when the host moves about in carrying out its normal life functions. The proliferation of implanted cells and the growth of vascular structures also contributes to the physiological stresses close to the boundary **16**. The stresses challenge the physical integrity of the boundary **16** by stretching or otherwise deforming it. Absent a sufficient ultimate strength value, normal physiological stresses can rupture the boundary **16**, exposing the implanted cells to the full effect of the host's immune and inflammatory systems.

The inventors presently believe that ultimate strength values sufficient to withstand physiological stresses close to the host tissue without rupture in animals lie above about 100 pounds per square inch (PSI). The ultimate strength values are determined by measuring the tensile strength of the material. Tensile strength is measured by ASTM D-412.

Also regardless of the type of implanted cell, the boundary **16** must possess a permeability profile that sustains a flux of nutrients into the chamber **12** and waste products from the chamber **12** sufficient to sustain the viability of the implanted cells.

Regardless of the particular mechanical configuration of the assembly **10** and **10'**, in the illustrated and preferred embodiment (which FIGS. **3** and **3A** best show), the permeable boundary **16** comprises a first permeable region **18**, a second permeable region **20**, and a third region **22** between the first and second regions **18** and **20**. According to one aspect of the invention, the third region **22** is formed-in-place between the other regions **18** and **20**, creating a robust, integrated boundary **16**. Furthermore, the parameters for manufacturing the formed-in-place integrated, three-region boundary **16** can also be controlled to provide the permeability profile required to sustain allografts and isografts. As will be pointed out later, FIGS. **3/3A/B** and **9** to **11** exaggerate the relative proportions of the various regions **18**, **20**, and **22** for the sake of illustration. FIG. **12** is an actual micrograph of a formed-in-place laminated structure that embodies the features of the invention, which more accurately shows the relative proportions of the various layers **18**, **20**, and **22** in a preferred implementation.

The assembly **10'** shown in FIGS. **2A** and **3A/B** represents a preferred embodiment because of the presence of a port member **15**, which provides means for accessing the interior chamber **12**. An elongated flexible tube **17** extends from the port member **15**, through which a syringe can be inserted to place cells in the chamber **12**, either before implantation, or after implantation, or to recharge the chamber **12** during implantation. Further details of the construction of the assembly **10'** are found in copending U.S. application Ser. No. 08/179,860, filed Jan. 11, 1994.

In the illustrated and preferred embodiment, each assembly **10** **10'** also includes written instructions **11** (see FIG. **1**) that teach the enclosure of living cells within the chamber **12** and the implantation of the chamber **12** with enclosed living cells in host tissue. Exemplary procedures for preparing the device for implanting and for implanting the device with living cells in host tissue are set forth in Section III(c) of this Specification.

A. The First Permeable Region

The first permeable region **18** immediately surrounds the chamber **12** containing the implanted cells **14**. The first region **18** possesses multiple characteristics.

Regardless of the type of implanted cell **14** (i.e., xenogeneic, allogeneic, or isogeneic), the first region **18** has a pore size sufficient to block penetration into the lumen of the chamber **12** by host cells. This penetration breaches the integrity of the boundary **16**, exposing the implanted cells **14** to the complete immune response of the host. Generally speaking, pore sizes less than about 2 μm (i.e., 2 micrometers) will block the ingress of vascular structures. As used in this Specification, "pore size" refers to the maximum pore size of the material. The practitioner determines pore size using conventional bubble point methodology, as described in Pharmaceutical Technology, May 1983, pages 36 to 42.

When the implanted cells are from the same animal species but have a different genetic make up (i.e., allografts), the pore size of the first region **18** usually must be sufficient to prevent the passage of inflammatory cells from the host into the implant cell chamber. In allografts, molecular immunogenic factors do not seem to adversely affect the viability of the implanted cells. Still, some degree of tissue matching may be required for complete protection. Pore sizes sufficient to block passage of inflammatory cells in humans lie in the range of below about 0.6 micrometers. These pore sizes, too, are impermeable to vascular structures. As used in this Specification, "inflammatory cells" include macrophages, foreign body giant cells, and fibroblasts, and "molecular immunogenic factors" refers to molecules such as antibodies and complement.

When the implanted cells are isografts (autologous implants of genetically engineered cells), the pore size must be sufficient only to prevent the isografts from exiting the chamber **12**, which also prevents ingress of vascular structures in the chamber **12**.

In a preferred embodiment, a permeable PTFE membrane material having a thickness of about 25 microns and a maximum pore size of about 0.4 micron is selected for the first region **18**. This material is commercially available from Millipore Corporation under the tradename Biopore™. This material has a thickness of about 25 microns and an ultimate (tensile) strength value of at least 3700 PSI, which is well above the desired minimum value. The selected material has a maximum pore size of 0.35 microns, which blocks the passage of inflammatory cells.

It should be appreciated that other, comparable materials can meet the stated requirements for the first region **18**. For example, polyethylene, polypropylene, cellulose acetate, cellulose nitrate, polycarbonate, polyester, nylon, and polysulfone materials, cellulose, polyvinylidene difluoride, acrylic, silicone, and polyacrylonitrile can be used.

B. The Second Permeable Region

The second permeable region **20** of the boundary overlies at least a portion of the first region **18**. The second region **20** constitutes an interface with host tissue.

In the illustrated and preferred embodiment, the second region **20** has an architecture that promotes the growth of vascular structures in host tissue near the interface. Preferably, at least some of the near vascular structures lie within one cell thickness of the interface.

It is through the second region **20** that the permeable boundary **16** associates itself with the host's biological system closely enough to transfer nutrients and wastes in support of the biological processes of the implanted cells **14**. The permeable boundary **16** also transfers the therapeutic products generated by the implanted cells **14** to the host.

Vascularization near the host tissue-boundary interface occurs if the three dimensional conformation of second region **20** promotes certain host inflammatory cell behavior. Brauker et al. have demonstrated that membranes that did have near vascular structures allowed cellular penetration and had pores that were formed by membrane structures (strands or fibers) with a diameter of less than 5 μm, whereas membranes that did not develop close vascular structures had cavities with "plate-like" qualities, having diameters greater than 5 μm. Histological examination of the vascularizing membranes revealed that the invading cells had a rounded morphology, while the cells were flattened in the membranes that did not have close vascular structures. The cells appear to be "trapped" and not allowed to flatten on any surface, which apparently causes the more rounded morphology of the cells which infiltrate the vascularizing membranes. The hypothesis is that the membrane architecture dictates cellular morphology, and the rounded cells in turn secrete some, as yet unknown, trophic factors which promote the formation of vascular structures.

Accordingly, the material for the second region **20** is a polymer membrane having an average nominal pore size of approximately 0.6 to about 20 μm, using conventional methods for determination of pore size in the trade.

Preferably, at least approximately 50% of the pores of the membrane have an average size of approximately 0.6 to about 20 μm.

The structural elements which provide the three dimensional conformation may include fibers, strands, globules, cones or rods of amorphous or uniform geometry which are smooth or rough. These elements, referred to generally as "strands," have in general one dimension larger than the other two and the smaller dimensions do not exceed five microns.

In one arrangement, the material consists of strands that define "apertures" formed by a frame of the interconnected strands. The apertures have an average size of no more than about 20 μm in any but the longest dimension. The apertures of the material form a framework of interconnected apertures, defining "cavities" that are no greater than an average of about 20 μm in any but the longest dimension.

In this arrangement, the material for the second region **20** has at least some apertures having a sufficient size to allow at least some vascular structures to be created within the cavities. At least some of these apertures, while allowing vascular structures to form within the cavities, prevent connective tissue from forming therein because of size restrictions.

Further details of the material are set forth in copending U.S. application Ser. No. 08/210,068 entitled "Close Vascularization Implant Material" filed Mar. 17, 1994, which is incorporated into this Specification by reference.

In a preferred implementation, the second region **20** comprises a membrane material made by W. L. Gore and Associates (Elkton, Md.) under the trade name Gore-Tex™. The Gore-Tex™ material comprises a microporous membrane made from PTFE. The membrane is 15 microns thick and has a pore size of 5 microns.

In another embodiment (not shown), the second region **20** comprises a permeable membrane structure formed with multiple microfabricated layers of polymer film made, for example, from photoimageable polyimide material. The film is processed, using either negative photoresist techniques or etchable membrane fabrication techniques, to create predefined geometric patterns of holes and intermediate spaces defining strands. The geometric patterns alternate between film layers from smaller, more closely spaced hole patterns (with cross hole dimensions equal to or less than about 20 μm and strand dimensions typically about 2–3 μm) to larger holes with less closely spaced patterns (with cross hole dimensions exceeding 20 μm and upwards to about 50 μm and strand dimensions typically about 4–5 μm). The stacking of different geometric patterns creates an open, permeable membrane structure having randomly positioned, interconnected cavities with minimum interior dimensions greater than about 5 μm formed by interconnected stands with minimum dimensions less than about 5 μm.

Further details of this construction are described in copending U.S. application Ser. No. 08/320,199 entitled "Porous Microfabricated Polymer Membrane Structure" filed Oct. 7, 1994, which is incorporated into this Specification by reference.

C. The Third Region

The third region **22** is located between the first and second regions **18** and **20**. According to the invention, the third region is formed-in-place between the two other regions **18** and **20**. As will be described in greater detail later, the formed-in-place third region **22** can be manufactured from natural or synthetic biocompatible polymers which, when cast, present a permeability and immunoisolation profile comparable to the first region **18**.

The preferred embodiment shows the permeable membrane structure being used in association with a chamber for implanting living cells. Still, it should be appreciated that the permeable structure embodying the features of the invention can be used in association with other implanted objects, like catheters, biosensing devices, and the like, which can be carried within the permeable boundary **16** in generally the same fashion as the living cells shown in the drawings.

II. Manufacture of the Permeable Boundary

The permeable boundary **16** functions as a synthetic membrane between host tissue and the cells **14** contained in the chamber **12**. With a concentration gradient as the driving force, the boundary membrane permits the selective transport of certain molecular solutes between host tissue and the cells **14**, while blocking the transport of other molecular solutes. The nature of the transport and blockage functions depends on prescribed, discriminating interactions between the physical configuration of the membrane and the physical configuration of the transported material. For synthetic membranes these interactions are based for the most part on the size of the transported material relative to the size and distribution of the passageways or pores within the membrane. In synthetic membranes, the size of the membrane pores often varies, sometimes over a broad range. In addition, the diffusion process within the various membrane pores can be significantly hindered relative to that in free solution by interactions of the solute with the pore walls, even when the solute is several times smaller than the pore.

The criteria in developing an immunoisolating membrane includes the creation of a structure for which (i) the largest pore will prohibit passage of a defined type or types of solute, and (ii) the distribution of pore size has a mean sufficiently close to the maximum pore size so that the diffusion of the desired small solutes is not overly hindered by a large population of very small pores.

The third region **22** is made by a process of controlled phase change, called "casting," in which the membrane material, a high molecular weight synthetic polymer, is first dissolved in a solvent, then applied upon the either one of the first or second permeable region **18** or **20**, with the other permeable region then laid on top, and then exposed to conditions which cause the material to precipitate from solution in a macroscopically continuous phase on the third region **22**. Careful selection and control of membrane material, solvent system, concentration, and phase inversion conditions determine the final membrane micro-architecture and permeability.

The polymer material for the third region **22** can comprise a natural or synthetic polymer selected based upon considerations that include its biocompatibility, its ease of fabrication, its ability to consistently form predictable, identifiable geometries and distributions, its chemical inertness, and its strong mechanical properties. For example, poly (ethylene-co-vinyl alcohol) (EVOH) is a polymer that meets the above criteria. However, it should be appreciated that other natural and synthetic polymers, for example, cellulose acetate (CA), poly(vinylidene difluoride) (PVDF), and ethyl vinyl alcohol (EVA) meet these criteria, as well, as do silicone, ceramic materials, and other elastomer and thermoplastic materials.

FIGS. **4** to **11** show the steps in the casting process performed in accordance with the invention. These steps are performed, regardless of the particular polymer selected.

The membrane casting process is preferably carried out in an enclosed casting chamber **24** (see FIG. **4**) beneath a standard laboratory fume hood. The casting chamber **24** permits the continuous flow of filtered air over the casting area.

Present within the casting chamber **24** (see FIG. **5**) are a casting plate **26**, a casting blade **28**, a syringe **30** containing dissolved polymer dope, a quenching bath **32**, and a rinsing bath **34**. The first and second membrane regions **18** and **20** are also handled within the casting chamber **24**.

The casting plate **26** is preferably polished stainless steel, but it can also be mirror glass. Its dimensions can vary. In one representative embodiment, the casting plate **26** (including an associated stretching frame) measures 6.4 inch by 10.1 inch, with a thickness of about 0.25 inch.

The plate **26** is cleaned, either with Contrad 70 (Curtin-Matheson Scientific) for steel or Chromerge (Mallinckrodt) for glass, rinsed thoroughly, dried in open air, flushed with filtered air, and then placed immediately into the casting chamber **24**.

Referring now to FIGS. **5** and **6**, the second permeable region **20** (for example, the GORE-TEX™ material described above) is peripherally secured to the casting plate **26** within the casting chamber **24**, using tape **36**, adhesive, or both. The side of the region **20** which, when implanted, faces implanted host tissue lies face down on the casting plate **26**. It is important that the second region **20** lays in intimate surface contact against the entire casting plate **26**, and that the region **20** is free of wrinkles. In this regard, it may be necessary to first stretch the region **20** on a stretching frame (not shown) before placing it on the plate **26**. The casting plate **26** may also be made with a slightly convex surface to assure intimate surface contact, particularly between the midportion of the plate **26** and the second region **20**.

The syringe **30** contains the polymer material selected for the third region **22**, which is dissolved in dope form in a selected solvent. The details of the dissolution process will vary according to the polymer used.

For example, EVOH is available in various molecular weights and monomer ratios from EVAL Company of America. The E-series material, containing 44 mole % ethylene, is used; however, other mole % ethylene EVOH materials can be used. To make a suitable batch, a desired weight percent of the EVOH material is weighed out into a small bottle. A desired weight percent of polyvinylpyrrolidone (PVP) is added to achieve the desired viscosity. An organic solvent like dimethylsulfoxide (DMSO) is added to make up the remaining weight percent. The solids are allowed to dissolve as the bottle is rotated at room temperature. Rotation assures proper adhesive dissolution and uniformity. The bottle is rotated until all solids are dissolved, typically up to 20 hours. Concentrations of from about 3 wt % to 8 wt % EVOH and from 2 wt % to 8 wt % PVP are recommended to serve as the formed-in-place third region **22**. Other higher or lower weight percentages can be used, depending upon processing conditions. After complete dissolution, the solution is cooled and pressure filtered prior to use.

After dissolution, the polymer dope is drawn up into the syringe **30** (which can be a 5 cc polypropylene syringe manufactured by Becton-Dickinson). The syringe **30** is capped, flushed with filtered air, and quickly placed in the casting chamber **24**.

As FIG. **7** shows, within the casting chamber **24**, the polymer dope is manually dispensed from the syringe **30** in an elongated bead **38** (typically about ⅛-inch in diameter, or about 1 to 2 cc) along the upper portion of the second region **20** on the casting plate **26**. As FIG. **8** shows, the dope bead **38** is then spread out or "drawn down" over the surface of the second region **20** by slowly dragging the casting blade **28** along the length of the plate **26** at a steady rate of about 10 to 20 inches per minute.

The thickness of the dope drawn down on the second region **20** depends upon the size of the gap that separates the edge of the casting blade **28** from the exposed surface of the second region **20**. The size of the gap can vary between depending upon the polymer used and the thickness desired. Using EVOH polymer dope, a gap of between 1.0 to 5.0 mil is recommended.

It is desirable that a portion of the polymer dope actually penetrates the surface of the second region **20** to some extent. This penetration further enhances the presence of a secure, physical bond to hold the first and second regions **18** and **20** together. Depending upon the surface tension characteristics of the second region **20** and the cast polymer used, it may be necessary to pretreat the second region **20** with a water soluble surfactant like FC-135, Pluronic, or Triton X100, before applying the dope bead. Other fluorosurfactants can be used. The pretreatment controls the adhesion and depth of penetration of the drawn-down dope by altering the hydrophility of the second region **20**. For example, pretreating the PTFE surface of a GORE-TEX material with a 0.1% to 0.2% FC-135 solution can be accomplished before casting with an EVOH polymer, although it is believed that such pretreatment is not critical to the overall process when using an EVOH polymer.

The desired degree of penetration can be controlled by balancing between the viscosity of the polymer dope (controlled by adding PVP) and the surface characteristics of the second region **20** (controlled by using surfactant and the like).

As FIG. **9** shows, once the polymer dope has been drawn down along the entire second region **20**, the first region **18** (for example, the BIOPORE™ material described above) is laid upon the casting plate **26** in intimate contact with the drawn-out dope polymer region **22**. The drawn down dope polymer region **22** will tend to stick immediately upon contact with the first region **18**. For this reason, it is recommended that a plastic film (such as PP2500 transparent film sold by 3M) be laid on top of the first region **18**, so that a smooth, consistent pressure against the first region **18** can be applied, starting with initial contact at the center and working from there outward. As the entire first region **18** is wetted out in the dope polymer, the plastic film can be removed.

Once the tri-layer laminate **40** is assembled on the casting plate **26** (as FIG. **10** shows), the casting plate **26** is lifted and slid smoothly into the quenching bath **32**. The contents of the quenching bath **32** will vary according to the polymer used. For EVOH polymer, the quenching bath **32** can comprise ethanol (EtOH), or reagent alcohol (RA), or water (H2O), or mixtures of water and DMSO (the recommended ratio being 75% H2O and 25% DMSO). Other solvent systems can be used. The quenching bath **32** is preferably maintained at a temperature of between 20° C. and 25° C. when EVOH polymers are being cast. Depending upon the solvent system and the permeability desired, the temperature range can vary.

The EVOH polymer is insoluble in the quenching bath **32**, whereas the PVP, organic solvent, and penetrating agents like surfactant are all soluble in the bath **32**. The permeable structure of the third region **22** thus forms in the quenching bath **32**. The bond between the third region **22** and the first and second regions **18** and **20** also forms in the quenching bath **32**. The permeable structures prepared from the polymer solutions, as above described, can be broadly classified as hydrogels in the sense that, in the presence of water, they form highly solvated, three dimensional, permeable networks with local regions of close molecular association which provide strength to the network.

After a prescribed period of time (usually at least 30 minutes), the plate **26** and tri-layer cast laminate **40** are removed as a unit from the quenching bath **32**. The tri-layer cast laminate **40** is gently removed from the casting plate **26**, as FIG. **11** shows. It is then allowed to float freely in a water wash bath **34** for a prescribed period of time (usually for 20 to 24 hours) to remove fillers, organic solvents, and penetrating agents. The temperature of the wash bath **34** is maintained at a temperature of about 37° C., however other temperatures can be used.

After washing, the tri-layer cast laminate structure **40** is carefully laid out and allowed to dry, at least overnight, before testing or use.

It should be appreciation that alternative methods could be used to apply the polymer dope.

In one alternative process (not shown), the dope bead **38** can be applied and drawn down directly on the first region **18** using the casting blade **28**, and the second region **20** laid on top. The tri-layer structure **40** is then placed in the quenching bath **32**, as previously described, followed by the subsequent water bath **34**, and drying, also as previously described.

In another alternative process (also not shown), the polymer dope can be applied without using a casting blade. In this process, a screen or template can be dipped in the polymer dope material and then laid upon the second region **20**. The dipped screen deposits a predetermined pattern of the polymer dope on the surface of the second region **20**, which remains upon removal of the screen. The first region **18** is then laid on top of the polymer dope pattern. The resulting tri-layer structure **40** is then placed in the quenching bath **32**, as previously described, followed by the subsequent water bath **34**, and drying, also as previously described.

It should also be appreciated that, by controlling the viscosity of the polymer dope (controlled by adding PVP) and the surface characteristics of the second region **20** (controlled by using surfactant and the like), as previously described, the polymer dope can be made to actually penetrate deeper into the permeable second region **20** (see FIG. **17**). Subsequent quenching, as already described, creates a formed-in-place permeable region **22'** located within the second region **20** (as FIG. **17** shows). The sub-surface region **22'** can itself serve as an immunoisolation barrier imbedded within the permeable region **20**, without the addition of the first region **18** or its equivalent. Alternatively (as FIG. **17** shows), the first region **18** or it eqivalent can also be affixed to the surface of the second region **20**, this time using a formed-in-place region **22** to laminate the first and second regions **18** and **20** together, or by some other lamination method.

The formed-in-place region can be located either on the surface of the second region **20** (as region **22**), where it serves also to bond the immunoisolation first region **18**, or within the second region **20** (as region **22'**) spaced away from the first region **18**. By tailoring the permeability of the formed-in-place regions **22** and **22'** to block penetration of host inflammatory cells, the invention makes possible the creation of a redundant immunoisolation barrier **45**, comprising multiple immunoisolation regions or layers **18**, **22'**, and (optionally) **22**. It should also be appreciation that the barrier **16** shown in FIGS. **3** and **3B** can also include redundant immunoisolation barriers, if the region **22**, like the region **18**, has a conformation that substantially blocks penetration of host inflammatory cells. The region **22** backs up the immunoisolation function of the first region **18**, and vice versa, in case of a manufacturing problem, failure due to handling, or while implanted. The invention therefore makes possible a redundant immunoisolation function without adversely affecting the overall permeability of the overall permeable structure.

III. Characterizing the Cast Laminated Structure

A. Morphology

FIG. **12** shows an actual micrograph of a representative tri-layer cast laminate **40** made according to the above-described process, examined using FE LVSEM analysis. The laminate **40** comprises 5 μm GORE-TEX™ material as the second region **20**; 0.4 μm BIOPORE™ PTFE material as the first region **18**; and a formed-in-place polymer comprising EVOH (3 wt % EVOH; 2% PVP; quenched in 100% ethanol) as the third region **22**. Analysis reveals that the formed-in-place EVOH layer **22** typically ranges from approximately 0.1 to 1.25 μm in thickness, but can be as much as 200 μm (it should thus be appreciated that preceding FIGS. **3** and **9** to **11** exaggerate the relative proportions of the various regions **18**, **20**, and **22** for the sake of illustration). As FIG. **12** shows, the cast EVOH layer **22** is typically also in substantially continuous, intimate contact with both the first and second regions **18** and **20**, and is sometimes observed to penetrate into both facing first and second regions **18** and **20** to a depth of several micrometers.

B. Permeability

Stirred diffusion cell and multi-solute permeability testing further reveals that the presence of the continuous formed-in-place layer **22** does not significantly reduce the overall permeability of the laminate to Tryptophan (Sigma T-0254) (0.5 mg/ml), Molecular Weight 204.2 D ;Vitamin B_{12} (Sigma V-2876) (1.5 mg/ml), Molecular Weight 1355 d; Myoglobin (Sigma M-0630) (6 mg/ml), Molecular Weight 17,000 d; Albumin (Sigma A-8022) (22 mg/ml), Molecular Weight 65,000 d; and IgG (Sigma I-5506) (25 mg/ml), Molecular Weight 160,000 d.

The following table lists the permeabilities of laminates of 0.4 μm BIOPORE™ PTFE material (abbreviated B in the Table) (comprising the first region **18**); a variety of EVOH formed-in-place polymers ranging between 3 wt % and 8% EVOH, blade gaps of 1.4 mil/2.8 mil/4.2 mil, and quenching baths comprising either EtOH or water (H2O) (comprising the third region **22**) (designated E-EtOH or E-H2O, depending upon the quenching bath); and 3 μm or 5 μm GORE-TEX™ materials (abbreviated G5 or G3) (comprising the second region **20**). The control laminate comprised 0.4 μm BIOPORE™ PTFE material laminated to 5 μm GORE-TEX™ material using EVA strands, as disclosed in U.S. Pat. No. 5,344,454. Permeabilities are express in terms of cm/sec$\times 10^{-4}$. Sample size is abbreviated S(n).

TABLE 1

Permeability of Cast Laminated Structures
(All values are x 10^{-4} cm/sec)

Laminate	L-Tryp	B_{12}	Myo	Alb	IgG
Control (S1)	NA	1.59	0.56	0.31	0.22
B/E-EtOH/5G (S52)	3.26 ± 0.53	1.83 ± 0.27	0.64 ± 0.09	0.35 ± 0.07	0.24 ± 0.06
B/F-H2O/G5 (S12)	3.40 ± 0.16	1.80 ± 0.13	0.59 ± 0.04	0.30 ± 0.03	0.21 ± 0.03

FIG. **13** is a log-graph that compares the permeability over a range of molecular weight solutes of the various cast laminates to the control and to 100 μm water. FIG. **13** demonstrates that the cast tri-layer laminates made accord-

ing to the invention are comparable to the control, which is known to possesses a range of permeabilities suited for at least allografts and isografts. FIG. **13** also demonstrates that the presence of the third region to bond the first and second regions together, does not significantly alter the permeability characteristics of the overall composite structure. In fact, Table 1 demonstrates that using the formed-in-place region, establishing intimate surface contact with the other regions, actually improves the permeability, compared to using EVA strands as the bonding agent (i.e., the control material).

Although the actual permeability of the formed-in-place layer **22**, $k_{m,22}$, cannot be measured directly, it can be estimated from the independently measured permeabilities of the adjacent layers **18** and **20** using the series mass transfer relationship:

$$\frac{1}{k_{m,22}} = \frac{1}{k_{m,40}} - \frac{1}{k_{m,18}} - \frac{1}{k_{m,20}}$$

where $k_{m,40}$, $k_{m,18}$, and $k_{m,20}$ are, respectively, the permeabilities of the laminate **40**, the second region **18**, and the first region **20**. Using an average vitamin B_{12} value from Table 1 of 1.82×10^{-4} cm/sec for $k_{m,40}$, and values for $k_{m,18}$ and $k_{m,20}$ of, respectively, 4.65×10^{-4} cm/sec and 3.75×10^{-4} cm/sec (obtained from separate studies), $k_{m,22}$ is found to be 14.8×10^{-4} cm/sec, over eight times the permeability of the entire laminate **40**.

C. Implantation Studies

Laminate **40** were formed using the above described methodology comprising 0.4 μm BIOPORE™ PTFE material as the first region **18**; a cast-in-place third region **22** comprising 3 wt % EVOH, 8 wt % PVP, 2% surfactant, cast using a 2.8 mil blade gap; and 5 μm GORE-TEX™ material as the second region **20**. The following Table 2 lists the permeability of the laminate **40** (six samples).

TABLE 2

Permeability of Implanted Cast Laminate
(All values are x 10^{-4} cm/sec)

L-Trp	B_{12}	Myo	Alb	IgG
2.7612 ± 0.2692	13588 ± 0.0778	0.2690 ± 0.0340	0.0624 ± 0.0166	0.0335 ± 0.0131

The six samples were formed into six ported devices of the configuration shown in FIGS. **2**A and **3**A/B, each having a 20 μl chamber for implanting living cells in host tissue. Ported devices were also made with the control membrane described above in connection with Table 1. The ported devices were assembled and sterilized with an overnight soak in 70% ethanol.

A first group of the devices made with the laminate **40** were implanted in the epididymal fat pads of Lewis rats, as were comparable devices made with the control membrane. In this group, the chambers were empty. This group will be called Group 1.

A second group of the devices made with the laminate **40** were implanted in epididymal fat pads of Lewis rats, as were comparable devices made with the control membrane. In this group, the chambers were filled via the port **15** with the same human fibroblast cell line. This group will be called Group 2, which comprised xenografts.

A third group of the devices made with the laminate **40** were implanted in epididymal fat pads of athymic (immune compromised) rats, as were comparable devices made with the control membrane. In this group, the chambers were filled via the port **15** with the same human fibroblast cell line. This group will be called Group 3.

The implants were removed after three weeks. Explanted devices were prepared for histology by standard methods and stained with hematoxylin and eosin. Sections were scored by three criteria:

(I) Tissue Survival within the Device (Tissue Score) (1=no survival to6=healthy, well differentiated epithelial tissue).

(ii) Host Response Outside the Device (Host Reaction) (1=low level reaction to 6=high reaction, macrophages and lymphocytes and plasma cells).

(iii) Membrane Delamination (Delamination), derived by measuring, for each device, the total linear distance about the midsection of each device (DTOT) and the linear distance in which the first and second regions of the associated membrane were separated by more than one cell layer (about 15 μm) (DSEP). Delamination is expressed as a percentage by dividing DSEP by DTOT.

The following Table 3 lists the histology results.

TABLE 3

Histology Results

Device	Tissue Score	Host Reaction	Delamination
Group 1 Control	NA	1.9 ± 0.5	20.9 ± 7.2
Group 1 Cast	NA	2.0 ± 0.4	4.9 ± 0.9
Group 2 Control	2.0 ± 0.0	5.8 ± 0.5	32.3 ± 11.5
Group 2 Cast	1.0 ± 0.0	4.4 ± 0.2	6.2 ± 3.2
Group 3 Control	4.0 ± 0.0	2.2 ± 0.3	13.7 ± 5.8
Group 3 Cast	4.0 ± 0.0	2.1 ± 0.2	6.8 ± 4.3

The Group 1 and Group 2 and Group 3 results all demonstrate that the host reaction to the cast laminate material is comparable to the host reaction to the control material, either without living cells and with living cells. The presence of the laminate region **22** does not itself create an added host response.

The Group 3 result demonstrates that the tissue scores for the cast laminate material are also comparable to the tissue scores for the control material. The presence of the laminate region does not effect the ability of the device to sustain living cells in host tissue.

The Group 1 and Group 2 and Group 3 results all demonstrate the superior resistance that the cast laminate material has to delamination, compared to the control membrane. Even in the presence of a strong host response (Group 2 xenografts), the cast laminate significantly reduced the incidence of delamination, compared to the control membrane.

FIG. **14** is an actual micrograph of a tri-layer cast laminate **40** made according to the invention after 10 weeks of implantation (without living cells) in a dog. FIG. **15** is a micrograph of the control membrane after 10 weeks of implantation (without living cells) in a dog. FIG. **14** shows the absence of delamination of the tri-layer cast structure, while FIG. **15** shows the presence of delamination in the control membrane structure, the area of delamination being indicated by the letter D in FIG. **15**. The cause of the delamination in FIG. **15** is the infiltration of host cells (indicated by the letter C in FIG. **15**) between the first and second regions **18** and **20**. FIG. **14** shows that the robust, integrated nature of the tri-layer cast laminated structure resists cellular infiltration into the formed-in-place third region, thereby preventing delamination of the overall boundary.

FIG. **16** is an actual micrograph of a tri-layer cast laminate **40** made according to the invention after 3 weeks of implan-

tation (without living lung tissue cells **14**) in a rat. Like FIG. **14**, FIG. **16** shows that the robust, integrated nature of the tri-layer cast laminated structure resists cellular infiltration into the formed-in-place third region, thereby preventing delamination of the overall boundary.

The demonstrated ability of third region **22** to resist delamination is not necessarily related to having an inherently high mechanical peel strength. The inventors have observed that host cells, once able to enter into a discontinuous space between the first and second regions **18** and **20**, proceed to tear the first and second regions **18** and **20** apart (as FIG. **15** shows), even in the presence of a laminating material lending a high peel strength. The inventors believe that the third region **22** resists delamination because of its substantially formed-in-place, continuous configuration between the first and second regions **18** and **20** (as FIGS. **14** and **16** show). This configuration eliminates the presence of spaces and discontinuities between the first and second regions **18** and **20**. As a result, the infiltration of host cells is considerably reduced. The formed-in-place, continuous configuration between the first and second regions **18** and **20** (as FIGS. **14** and **16** show). This configuration eliminates the presence of spaces and discontinuities between the first and second regions **18** and **20**. As a result, the infiltration of host cells is considerably reduced. The formed-in-place laminate thus resists delamination, even should it not possess a high mechanical peel strength.

Various features of the invention are set forth in the following claims.

We claim:

1. A permeable structure forming a chamber to hold living cells, the permeable structure comprising a first permeable region surrounding at least a portion of the chamber having a conformation that, when implanted in host tissue, substantially blocks penetration of host cells into the chamber while permitting solute transport between the host and cells, a second permeable region overlying the first permeable region having a conformation that, when implanted in host tissue, forms a permeable interface with host tissue that permits solute transport between the host and cells, and a third permeable region between the first and second permeable regions comprising polymer material layer formed in place between the first and second permeable regions, the third permeable region bonding the first and second permeable regions together and having a conformation that, when implanted in host tissue, permits solute transport between the first and second permeable regions.

2. A permeable structure forming a chamber to hold living cells, the permeable structure comprising a first permeable region surrounding at least a portion of the chamber having a conformation that, when implanted in host tissue, substantially blocks penetration of host cells into the chamber while permitting solute transport between the host and cells, a second permeable region overlying the first permeable region having a conformation that, when implanted in host tissue, forms a permeable interface with host tissue that promotes the growth of vascular structures near the permeable interface while permitting solute transport between the host and cells, and a third permeable region between the first and second permeable regions comprising a polymer material layer formed in place between the first and second permeable regions, the third permeable region bonding the first and second permeable regions together and having a conformation that, when implanted in host tissue permits solute transport between the first and second permeable regions.

3. A permeable structure forming a chamber to hold living cells, the permeable structure comprising a first permeable region surrounding at least a portion of the chamber having a conformation that, when implanted in host tissue, substantially blocks penetration of host cells into the chamber while permitting solute transport between the host and cells, a second permeable region overlying the first permeable region having a conformation that, when implanted in host tissue, forms a permeable interface with host tissue that permits solute transport between the host and cells, the first permeable region comprising an array of three dimensional strands having a first dimension larger than a second and third dimensions and, for the majority of strands, neither of the second and third dimensions exceeds about 5 μm, and a third permeable region between the first and second permeable regions comprising a polymer material layer formed in place between the first and second permeable regions, the third permeable region bonding the first and second permeable regions together and having a conformation that, when implanted in host tissue, permits solute transport between the first and second permeable regions.

4. A permeable structure according to claim **1** or **2** or **3** wherein the conformation of the first permeable region, when implanted in host tissue, substantially blocks penetration of at least host tissue inflammatory cells into the chamber.

5. A permeable structure according to claim **4** wherein the conformation of the third permeable region, when implanted in host tissue, substantially blocks penetration of at least host tissue inflammatory cells into the chamber.

6. A permeable structure according to claim **1** or **2** or **3** wherein the third permeable region is in substantially continuous, intimate contact with the first and second permeable regions to substantially block infiltration of host cells between the first and second permeable regions.

7. A permeable structure according to claim **1** or **2** or **3** wherein the third permeable region penetrates at least partially into at least one of the first and second permeable regions.

8. A permeable structure according to claim **1** or **2** or **3** wherein the third permeable region has a thickness of between about 0.1 μm and 20 μm.

9. A permeable structure according to claim **1** or **2** or **3** wherein the polymer material of the third permeable region is selected from a group consisting essentially of poly (ethylene-co-vinyl alcohol), cellulose acetate, and poly (vinylidene difluoride).

10. A permeable structure according to claim **1** or **2** or **3** wherein the polymer material of the third permeable region comprises poly(ethylene-co-vinyl alcohol).

11. A permeable structure according to claim **10** wherein the polymer material of the third permeable region comprises about 3% to about 8% by weight of poly(ethylene-co-vinyl alcohol).

12. A permeable structure according to claim **1** or **2** or **3** wherein the permeable structure has a determinable first permeability value, wherein the third region has a determinable second permeability value, and wherein the second permeability is at least twice the first permeability value.

13. A permeable structure according to claim **1** or **2** or **3** and further comprising living cells in the chamber.

14. A permeable structure according to claim **13** wherein the living cells are allogeneic with respect to host tissue.

15. A permeable structure according to claim **13** wherein the living cells are isogeneic with respect to host tissue.

16. A permeable structure according to claim **1** or **2** or **3** and further comprising instructions teaching enclosure of living cells within the chamber and implantation of the permeable structure with enclosed living cells in host tissue.

17. A permeable structure forming a chamber to hold living cells, the structure comprising a permeable layer surrounding the chamber that, when implanted in host tissue, blocks contact between cells in the chamber and host cells while permitting transport of solutes between the host and cells, the permeable layer comprising a first immunoisolation region having a conformation that, when implanted in host tissue, substantially blocks penetration of host inflammatory cells, and a second immunoisolation region distinct from the first region, the second region having a conformation that, when implanted in host tissue, also substantially blocks penetration of host inflammatory cells, the first and second regions being mutually arranged in the permeable layer to together provide a redundant immunoisolation barrier.

18. A permeable structure according to claim 17 wherein the first and second immunoisolation regions contact each other in the layer.

19. A permeable structure according to claim 17 wherein the first and second immunoisolation regions are spaced apart in the layer.

20. A permeable structure according to claim 17 wherein the first immunoisolation region is formed in place in contact with the second immunoisolation region.

21. A permeable structure according to claim 17 wherein the first immunoisolation region is cast in contact with the second immunoisolation region and coagulated in place in contact with the second immunoisolation region.

22. A permeable structure forming a chamber to hold living cells, the structure comprising a permeable membrane surrounding the chamber having a conformation that, when implanted in host tissue, substantially blocks penetration of at least host inflammatory cells into the chamber while permitting solute transport between the host and cells, the permeable membrane having a surface, and an auxiliary permeable layer bonded in substantially continuous contact with the permeable membrane surface to substantially block infiltration of host cells between the auxiliary permeable layer and the permeable surface, the auxiliary permeable layer having a conformation that, when implanted in host tissue, substantially blocks penetration of at least host inflammatory cells while permitting solute transport through the permeable membrane.

23. A permeable structure forming a chamber to hold living cells, the structure comprising a permeable membrane surrounding the chamber having a conformation that, when implanted in host tissue, substantially blocks penetration of at least host inflammatory cells into the chamber while permitting solute transport between the host and cells, the permeable membrane having a surface, and an auxiliary permeable layer comprising a solution of polymer material brought into contact with the permeable membrane surface and formed in place on the permeable membrane surface, the auxiliary permeable layer having a conformation that, when implanted in host tissue, substantially blocks penetration of at least host inflammatory cells while permitting solute transport through the permeable membrane.

24. A permeable structure according to claim 23 wherein the auxiliary permeable layer is in substantially continuous, intimate contact with the permeable membrane surface to substantially block infiltration of host cells between the auxiliary permeable layer and the permeable membrane surface.

25. A permeable structure according to claim 22 or 23 wherein the auxiliary permeable layer penetrates at least partially into the permeable membrane surface.

26. A permeable structure according to claim 22 or 23 wherein the polymer material of the auxiliary permeable layer is selected from a group consisting essentially of poly(ethylene-co-vinyl alcohol), cellulose acetate, and poly (vinylidene difluoride).

27. A permeable structure according to claim 22 or 23 wherein the polymer material of the auxiliary permeable layer comprises poly(ethylene-co-vinyl alcohol).

28. A permeable structure according to claim 27 wherein the polymer material of the auxiliary permeable layer comprises about 3% to about 8% by weight of poly(ethylene-co-vinyl alcohol).

29. A permeable structure according to claim 22 or 23 and further comprising living cells in the chamber.

30. A permeable structure according to claim 29 wherein the living cells are allogeneic with respect to host tissue.

31. A permeable structure according to claim 29 wherein the living cells are isogeneic with respect to host tissue.

32. A permeable structure according to claim 22 or 23 and further comprising instructions teaching enclosure of living cells within the chamber and implantation of the permeable structure with enclosed living cells in host tissue.

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